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(54) Title: ACYLATED PIPERIDINE DERIVATIVES AS MELANOCORTIN-4 RECEPTOR AGONISTS

(57) Abstract: Certain novel 4-substituted N-acylated piperidine derivatives are agonists of the human melanocortin receptor(s) and, in particular, are selective agonists of the human melanocortin-4 receptor (MC-4R). They are therefore useful for the treatment, control, or prevention of diseases and disorders responsive to the activation of MC-4R, such as obesity, diabetes, sexual dysfunction, including erectile dysfunction and female sexual dysfunction.

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TITLE OF THE INVENTION

ACYLATED PIPERIDINE DERIVATIVES AS MELANOCORTIN-4 RECEPTOR AGONISTS

5 FIELD OF THE INVENTION

The present invention relates to acylated piperidine derivatives, their synthesis, and their use as melanocortin receptor (MC-R) agonists. More particularly, the compounds of the present invention are selective agonists of the melanocortin-4 receptor (MC-4R) and are thereby useful for the treatment of disorders responsive to
10 the activation of MC-4R, such as obesity, diabetes, male sexual dysfunction, and female sexual dysfunction.

BACKGROUND OF THE INVENTION

Pro-opiomelanocortin (POMC) derived peptides are known to affect
15 food intake. Several lines of evidence support the notion that the G-protein coupled receptors (GPCRs) of the melanocortin receptor (MC-R) family, several of which are expressed in the brain, are the targets of POMC derived peptides involved in the control of food intake and metabolism. A specific single MC-R that may be targeted for the control of obesity has not yet been identified, although evidence has been
20 presented that MC-4R signalling is important in mediating feed behavior (S.Q. Giraudo et al., "Feeding effects of hypothalamic injection of melanocortin-4 receptor ligands," Brain Research, 80: 302-306 (1998)).

Evidence for the involvement of MC-R's in obesity includes: i) the agouti (A^y) mouse which ectopically expresses an antagonist of the MC-1R, MC-3R
25 and -4R is obese, indicating that blocking the action of these three MC-R's can lead to hyperphagia and metabolic disorders; ii) MC-4R knockout mice (D. Huszar et al., Cell, 88: 131-141 (1997)) recapitulate the phenotype of the agouti mouse and these mice are obese; iii) the cyclic heptapeptide MT-II (a non-selective MC-1R, -3R, -4R, and -5R agonist) injected intracerebroventricularly (ICV) in rodents, reduces food
30 intake in several animal feeding models (NPY, *ob/ob*, agouti, fasted) while ICV injected SHU-9119 (MC-3R and 4R antagonist; MC-1R and -5R agonist) reverses this effect and can induce hyperphagia; iv) chronic intraperitoneal treatment of Zucker fatty rats with an α -NDP-MSH derivative (HP228) has been reported to activate MC-1R, -3R, -4R, and -5R and to attenuate food intake and body weight gain over a 12-
35 week period (I. Corcos et al., "HP228 is a potent agonist of melanocortin receptor-4

and significantly attenuates obesity and diabetes in Zucker fatty rats," Society for Neuroscience Abstracts, 23: 673 (1997)).

Five distinct MC-R's have thus far been identified, and these are expressed in different tissues. MC-1R was initially characterized by dominant gain of function mutations at the Extension locus, affecting coat color by controlling phaeomelanin to eumelanin conversion through control of tyrosinase. MC-1R is mainly expressed in melanocytes. MC-2R is expressed in the adrenal gland and represents the ACTH receptor. MC-3R is expressed in the brain, gut, and placenta and may be involved in the control of food intake and thermogenesis. MC-4R is uniquely expressed in the brain, and its inactivation was shown to cause obesity (A. Kask, et al., "Selective antagonist for the melanocortin-4 receptor (HS014) increases food intake in free-feeding rats," Biochem. Biophys. Res. Commun., 245: 90-93 (1998)). MC-5R is expressed in many tissues, including white fat, placenta and exocrine glands. A low level of expression is also observed in the brain. MC-5R knockout mice reveal reduced sebaceous gland lipid production (Chen et al., Cell, 91: 789-798 (1997)).

Erectile dysfunction denotes the medical condition of inability to achieve penile erection sufficient for successful sexual intercourse. The term "impotence" is oftentimes employed to describe this prevalent condition. Approximately 140 million men worldwide, and, according to a National Institutes of Health study, about 30 million American men suffer from impotency or erectile dysfunction. It has been estimated that the latter number could rise to 47 million men by the year 2000. Erectile dysfunction can arise from either organic or psychogenic causes, with about 20% of such cases being purely psychogenic in origin. Erectile dysfunction increases from 40% at age 40, to 67% at age 75, with over 75% occurring in men over the age of 50. In spite of the frequent occurrence of this condition, only a small number of patients have received treatment because existing treatment alternatives, such as injection therapies, penile prosthesis implantation, and vacuum pumps, have been uniformly disagreeable [for a discussion, see "ABC of sexual health - erectile dysfunction," Brit. Med. J. 318: 387-390 (1999)]. Only more recently have more viable treatment modalities become available, in particular orally active agents, such as sildenafil citrate, marketed by Pfizer under the brand name of Viagra®. (See "Emerging pharmacological therapies for erectile dysfunction," Exp. Opin. Ther. Patents 9: 1689-1696 (1999)). Sildenafil is a selective inhibitor of type V phosphodiesterase (PDE-V), a cyclic-GMP-specific phosphodiesterase isozyme [see

R.B. Moreland *et al.*, "Sildenafil: A Novel Inhibitor of Phosphodiesterase Type 5 in Human Corpus Cavernosum Smooth Muscle Cells," *Life Sci.*, 62: 309-318 (1998)]. Prior to the introduction of Viagra on the market, less than 10% of patients suffering from erectile dysfunction received treatment. Sildenafil is also being evaluated in the clinic for the treatment of female sexual dysfunction.

The regulatory approval of Viagra® for the oral treatment of erectile dysfunction has invigorated efforts to discover even more effective methods to treat erectile dysfunction. Several additional selective PDE-V inhibitors are in clinical trials. UK-114542 is a sildenafil backup from Pfizer with supposedly improved properties. Tadalafil or IC-351 (ICOS Corp.) is claimed to have greater selectivity for PDE-V over PDE-VI than sildenafil. Other PDE-V inhibitors include vardenafil from Bayer, M-54033 and M-54018 from Mochida Pharmaceutical Co., and E-4010 from Eisai Co., Ltd.

Other pharmacological approaches to the treatment of erectile dysfunction have been described [see, e.g., "Latest Findings on the Diagnosis and Treatment of Erectile Dysfunction," *Drug News & Perspectives*, 9: 572-575 (1996); "Oral Pharmacotherapy in Erectile Dysfunction," *Current Opinion in Urology*, 7: 349-353 (1997)]. A product under clinical development by Zonagen is an oral formulation of the alpha-adrenoceptor antagonist phentolamine mesylate under the brand name of Vasomax®. Vasomax® is also being evaluated for the treatment of female sexual dysfunction.

Drugs to treat erectile dysfunction act either peripherally or centrally. They are also classified according to whether they "initiate" a sexual response or "facilitate" a sexual response to prior stimulation [for a discussion, see "A Therapeutic Taxonomy of Treatments for Erectile Dysfunction: An Evolutionary Imperative," *Int. J. Impotence Res.*, 9: 115-121 (1997)]. While sildenafil and phentolamine act peripherally and are considered to be "enhancers" or "facilitators" of the sexual response to erotic stimulation, sildenafil appears to be efficacious in both mild organic and psychogenic erectile dysfunction. Sildenafil has an onset of action of 30-60 minutes after an oral dose with the effect lasting about 4 hours, whereas phentolamine requires 5-30 minutes for onset with a duration of 2 hours. Although sildenafil is effective in a majority of patients, it takes a relatively long time for the compound to show the desired effects. The faster-acting phentolamine appears to be less effective and to have a shorter duration of action than sildenafil. Oral sildenafil is effective in about 70% of men who take it, whereas an adequate response with

phentolamine is observed in only 35-40% of patients. Both compounds require erotic stimulation for efficacy. Since sildenafil indirectly increases blood flow in the systemic circulation by enhancing the smooth muscle relaxation effects of nitric oxide, it is contraindicated for patients with unstable heart conditions or cardiovascular disease, in particular patients taking nitrates, such as nitroglycerin, to treat angina. Other adverse effects associated with the clinical use of sildenafil include headache, flushing, dyspepsia, and "abnormal vision," the latter the result of inhibition of the type VI phosphodiesterase isozyme (PDE-VI), a cyclic-GMP-specific phosphodiesterase that is concentrated in the retina. "Abnormal vision" is defined as a mild and transient "bluish" tinge to vision, but also an increased sensitivity to light or blurred vision.

Synthetic melanocortin receptor agonists (melanotropic peptides) have been found to initiate erections in men with psychogenic erectile dysfunction [See H. Wessells et al., "Synthetic Melanotropic Peptide Initiates Erections in Men With Psychogenic Erectile Dysfunction: Double-Blind, Placebo Controlled Crossover Study," J. Urol., 160: 389-393 (1998); Fifteenth American Peptide Symposium, June 14-19, 1997 (Nashville TN)]. Activation of melanocortin receptors of the brain appears to cause normal stimulation of sexual arousal. In the above study, the centrally acting α -melanocyte-stimulating hormone analog, melanotan-II (MT-II), exhibited a 75% response rate, similar to results obtained with apomorphine, when injected intramuscularly or subcutaneously to males with psychogenic erectile dysfunction. MT-II is a synthetic cyclic heptapeptide, Ac-Nle-c[Asp-His-DPhe-Arg-Trp-Lys]-NH₂, which contains the 4-10 melanocortin receptor binding region common to α -MSH and adrenocorticotropin, but with a lactam bridge. It is a non-selective MC-1R, -3R, -4R, and -5R agonist (Dorr et al., Life Sciences, Vol. 58, 1777-1784, 1996). MT-II (also referred to as PT-14) (Erectide®) is presently in clinical development by Palatin Technologies, Inc. and TheraTech, Inc. as a non-penile subcutaneous injection formulation. It is considered to be an "initiator" of the sexual response. The time to onset of erection with this drug is relatively short (10-20 minutes) with a duration of action approximately 2.5 hours. Adverse reactions observed with MT-II include nausea, flushing, loss of appetite, stretching, and yawning and may be the result of activation of MC-1R, MC-2R, MC-3R, and/or MC-5R. MT-II must be administered parenterally, such as by subcutaneous, intravenous, or intramuscular route, since it is not absorbed into the systemic circulation when given by the oral route.

MT-II's erectogenic properties apparently are not limited to cases of psychogenic erectile dysfunction in that men with a variety of organic risk factors developed penile erections upon subcutaneous injection of the compound; moreover, the level of sexual desire was significantly higher after MT-II administration than after placebo [see H. Wessells, "Effect of an Alpha-Melanocyte Stimulating Hormone Analog on Penile Erection and Sexual Desire in Men with Organic Erectile Dysfunction," Urology, 56: 641-646 (2000)].

Compositions of melanotropic peptides and methods for the treatment of psychogenic erectile dysfunction are disclosed in U.S. Patent No. 5,576,290, assigned to Competitive Technologies. Methods of stimulating sexual response in females using melanotropic peptides have been disclosed in U.S. Patent No. 6,051,555.

Spiropiperidine and piperidine derivatives have been disclosed in WO 99/64002 (16 December 1999); WO 00/74679 (14 December 2000); WO 01/70708 (27 September 2001); WO 01/70337 (27 September 2001); and WO 01/91752 (6 December 2001) as agonists of the melanocortin receptor(s) and particularly as selective agonists of the MC-4R receptor and thereby useful for the treatment of diseases and disorders, such as obesity, diabetes, and sexual dysfunction, including erectile dysfunction and female sexual dysfunction.

Because of the unresolved deficiencies of the various pharmacological agents discussed above, there is a continuing need in the medical arts for improved methods and compositions to treat individuals suffering from psychogenic and/or organic sexual dysfunction. Such methods should have wider applicability, enhanced convenience and ease of compliance, short onset of action, reasonably long duration of action, and minimal side effects with few contraindications, as compared to agents now available.

It is therefore an object of the present invention to provide acylated piperidine derivatives which are melanocortin receptor agonists and thereby useful to treat obesity, diabetes, male sexual dysfunction, and female sexual dysfunction.

It is another object of the present invention to provide acylated piperidine derivatives which are selective agonists of the melanocortin-4 (MC-4R) receptor.

It is another object of the present invention to provide pharmaceutical compositions comprising the melanocortin receptor agonists of the present invention with a pharmaceutically acceptable carrier.

It is another object of the present invention to provide methods for the treatment or prevention of disorders, diseases, or conditions responsive to the activation of the melanocortin-4 receptor in a subject in need thereof by administering the compounds and pharmaceutical compositions of the present invention.

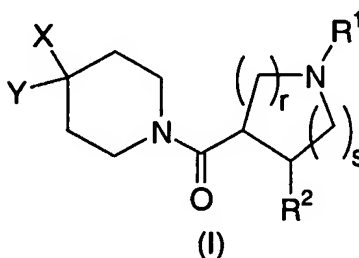
5 It is another object of the present invention to provide methods for the treatment or prevention of obesity, diabetes mellitus, male sexual dysfunction, and female sexual dysfunction by administering the compounds and pharmaceutical compositions of the present invention to a subject in need thereof.

10 It is another object of the present invention to provide methods for the treatment of erectile dysfunction by administering the compounds and pharmaceutical compositions of the present invention to a subject in need thereof.

These and other objects will become readily apparent from the detailed description that follows.

15 SUMMARY OF THE INVENTION

The present invention relates to novel 4-substituted N-acylated piperidines of structural formula I:



20 These acylated piperidine derivatives are effective as melanocortin receptor agonists and are particularly effective as selective melanocortin-4 receptor (MC-4R) agonists. They are therefore useful for the treatment and/or prevention of disorders responsive to the activation of MC-4R, such as obesity, diabetes as well as male and female sexual dysfunction, in particular, male erectile dysfunction.

25 The present invention also relates to pharmaceutical compositions comprising the compounds of the present invention and a pharmaceutically acceptable carrier..

The present invention also relates to methods for the treatment or prevention of disorders, diseases, or conditions responsive to the activation of the melanocortin receptor in a subject in need thereof by administering the compounds and pharmaceutical compositions of the present invention.

5 The present invention also relates to methods for the treatment or prevention of obesity, diabetes mellitus, male sexual dysfunction, and female sexual dysfunction by administering the compounds and pharmaceutical compositions of the present invention.

10 The present invention also relates to methods for treating erectile dysfunction by administering the compounds and pharmaceutical compositions of the present invention.

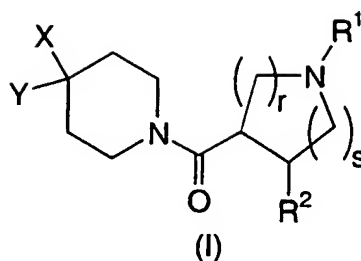
15 The present invention also relates to methods for treating erectile dysfunction by administering the compounds of the present invention in combination with a therapeutically effective amount of another agent known to be useful to treat the condition.

 The present invention also relates to methods for treating or preventing obesity by administering the compounds of the present invention in combination with a therapeutically effective amount of another agent known to be useful to treat or prevent the condition.

20 The present invention also relates to methods for treating or preventing diabetes by administering the compounds of the present invention in combination with a therapeutically effective amount of another agent known to be useful to treat or prevent the condition.

25 DETAILED DESCRIPTION OF THE INVENTION

 The present invention relates to 4-substituted N-acylated piperidine derivatives useful as melanocortin receptor agonists, in particular, as selective MC-4R agonists. Compounds of the present invention are described by structural formula I:



or a pharmaceutically acceptable salt thereof;

wherein

r is 1 or 2;

5 s is 0, 1, or 2;

n is 0, 1 or 2;

p is 0, 1, or 2;

R¹ is selected from the group consisting of

10 hydrogen,

amidino,

C₁₋₄ alkyliminoyl,

C₁₋₁₀ alkyl,

(CH₂)_n-C₃₋₇ cycloalkyl,

15 (CH₂)_n-phenyl,

(CH₂)_n-naphthyl, and

(CH₂)_n-heteroaryl wherein heteroaryl is selected from the group consisting of

(1) pyridinyl,

(2) furyl,

20 (3) thienyl,

(4) pyrrolyl,

(5) oxazolyl,

(6) thiazolyl,

(7) imidazolyl,

25 (8) pyrazolyl,

(9) isoxazolyl,

(10) isothiazolyl,

(11) pyrimidinyl,

(12) pyrazinyl,

- (13) pyridazinyl,
(14) quinolyl,
(15) isoquinolyl,
(16) benzimidazolyl,
5 (17) benzofuryl,
(18) benzothieryl,
(19) indolyl,
(20) benzthiazolyl, and
(21) benzoxazolyl;
- 10 in which phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R³; and alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R³ and oxo;
- 15 R² is selected from the group consisting of
phenyl,
naphthyl, and
heteroaryl wherein heteroaryl is selected from the group consisting of
- 20 (1) pyridinyl,
(2) furyl,
(3) thienyl,
(4) pyrrolyl,
(5) oxazolyl,
(6) thiazolyl,
25 (7) imidazolyl,
(8) pyrazolyl,
(9) isoxazolyl,
(10) isothiazolyl,
(11) pyrimidinyl,
30 (12) pyrazinyl,
(13) pyridazinyl,
(14) quinolyl,
(15) isoquinolyl,
(16) benzimidazolyl,
35 (17) benzofuryl,

- (18) benzothienyl,
- (19) indolyl,
- (20) benzthiazolyl, and
- (21) benzoxazolyl;

5 in which phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R³;

R³ is selected from the group consisting of

- C₁₋₆ alkyl,
- 10 (CH₂)_n-phenyl,
- (CH₂)_n-naphthyl,
- (CH₂)_n-heteroaryl,
- (CH₂)_n-heterocyclyl,
- (CH₂)_nC₃₋₇ cycloalkyl,
- 15 halogen,
- OR⁴,
- (CH₂)_nN(R⁴)₂,
- (CH₂)_nC≡N,
- CO₂R⁴,
- 20 C(R⁴)(R⁴)N(R⁴)₂,
- NO₂,
- (CH₂)_nNR⁴SO₂R⁴
- (CH₂)_nSO₂N(R⁴)₂,
- (CH₂)_nS(O)_pR⁴,
- 25 (CH₂)_nNR⁴C(O)N(R⁴)₂,
- (CH₂)_nC(O)N(R⁴)₂,
- (CH₂)_nNR⁴C(O)R⁴,
- (CH₂)_nNR⁴CO₂R⁴,
- CF₃,
- 30 CH₂CF₃,
- OCF₃, and
- OCH₂CF₃;

in which heteroaryl is as defined above; phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to three substituents

35 independently selected from halogen, hydroxy, C₁₋₄ alkyl, trifluoromethyl, and C₁₋₄

alkoxy; and $(CH_2)_n$ is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl;

each R^4 is independently selected from the group consisting of

- 5 hydrogen,
 C_{1-6} alkyl,
 $(CH_2)_n$ -phenyl,
 $(CH_2)_n$ -naphthyl, and
 $(CH_2)_n C_{3-7}$ cycloalkyl;

- 10 wherein cycloalkyl is unsubstituted or substituted with one to three groups independently selected from halogen, C_{1-4} alkyl, and C_{1-4} alkoxy;
 or two R^4 groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC_{1-4} alkyl;

15

each R^5 is independently selected from the group consisting of

- hydrogen,
 C_{1-8} alkyl,
 $(CH_2)_n$ -phenyl,
20 $(CH_2)_n$ -naphthyl,
 $(CH_2)_n$ -heteroaryl, and
 $(CH_2)_n C_{3-7}$ cycloalkyl;

- wherein heteroaryl is as defined above; phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^3 ;
25 and alkyl, cycloalkyl, and $(CH_2)_n$ are unsubstituted or substituted with one to three groups independently selected from R^3 and oxo; or two R^5 groups together with the atom to which they are attached form a 5- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC_{1-4} alkyl;

30

X is selected from the group consisting of

- C_{1-8} alkyl,
 $(CH_2)_n C_{3-8}$ cycloalkyl,
 $(CH_2)_n$ -phenyl,

- $(\text{CH}_2)_n$ -naphthyl,
 $(\text{CH}_2)_n$ -heteroaryl,
 $(\text{CH}_2)_n$ heterocyclyl,
 $(\text{CH}_2)_n\text{C}\equiv\text{N}$,
5 $(\text{CH}_2)_n\text{CON}(\text{R}^5\text{R}^5)$,
 $(\text{CH}_2)_n\text{CO}_2\text{R}^5$,
 $(\text{CH}_2)_n\text{COR}^5$,
 $(\text{CH}_2)_n\text{NR}^5\text{C}(\text{O})\text{R}^5$,
 $(\text{CH}_2)_n\text{NR}^5\text{CO}_2\text{R}^5$,
10 $(\text{CH}_2)_n\text{NR}^5\text{C}(\text{O})\text{N}(\text{R}^5)_2$,
 $(\text{CH}_2)_n\text{NR}^5\text{SO}_2\text{R}^5$,
 $(\text{CH}_2)_n\text{S}(\text{O})_p\text{R}^5$,
 $(\text{CH}_2)_n\text{SO}_2\text{N}(\text{R}^5)(\text{R}^5)$,
 $(\text{CH}_2)_n\text{OR}^5$,
15 $(\text{CH}_2)_n\text{OC}(\text{O})\text{R}^5$,
 $(\text{CH}_2)_n\text{OC}(\text{O})\text{OR}^5$,
 $(\text{CH}_2)_n\text{OC}(\text{O})\text{N}(\text{R}^5)_2$,
 $(\text{CH}_2)_n\text{N}(\text{R}^5)(\text{R}^5)$, and
 $(\text{CH}_2)_n\text{NR}^5\text{SO}_2\text{N}(\text{R}^5)(\text{R}^5)$;
- 20 wherein heteroaryl is as defined above; phenyl, naphthyl, and heteroaryl are
unsubstituted or substituted with one to three groups independently selected from R^3 ;
and alkyl, $(\text{CH}_2)_n$, cycloalkyl, and heterocyclyl are unsubstituted or substituted with
one to three groups independently selected from R^3 and oxo;
- 25 Y is selected from the group consisting of
hydrogen,
C₁₋₈ alkyl,
C₂₋₆ alkenyl,
 $(\text{CH}_2)_n\text{C}_{3-8}$ cycloalkyl,
30 $(\text{CH}_2)_n$ -phenyl,
 $(\text{CH}_2)_n$ -naphthyl,
 $(\text{CH}_2)_n$ -heteroaryl, and
 $(\text{CH}_2)_n$ -heterocyclyl;

wherein heteroaryl is as defined above, and phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^3 ; and alkyl, $(CH_2)_n$, cycloalkyl, and heterocyclyl are optionally substituted with one to three groups independently selected from R^3 and oxo.

5 In one embodiment of the compounds of structural formula I, R^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl, $(CH_2)_{0-1}C_{3-6}$ cycloalkyl, and $(CH_2)_{0-1}$ -phenyl; wherein phenyl is unsubstituted or substituted with one to three groups independently selected from R^3 ; and alkyl and cycloalkyl are optionally substituted with one to three groups independently selected from R^3 and oxo.

10 In a second embodiment of the compounds of structural formula I, R^2 is phenyl or thienyl optionally substituted with one to three groups independently selected from R^3 . In a class of this embodiment, R^2 is phenyl optionally substituted with one to three groups independently selected from R^3 .

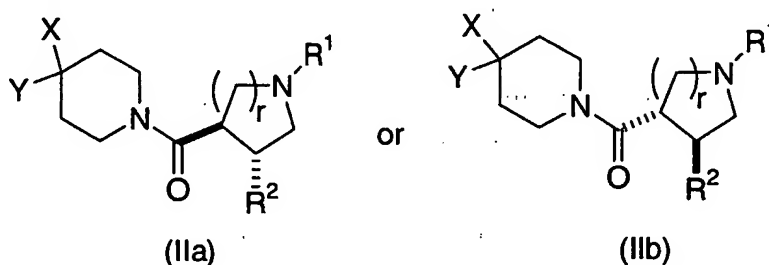
In a third embodiment of the compounds of structural formula I, X is
15 selected from the group consisting of C_{1-6} alkyl, $(CH_2)_n$ -phenyl, $(CH_2)_n$ -naphthyl, $(CH_2)_n$ -heteroaryl, $(CH_2)_n$ -heterocyclyl, $(CH_2)_nC(O)N(R^5)(R^5)$, $(CH_2)_nCO_2R^5$, $(CH_2)_nS(O)_pR^5$, $(CH_2)_nOR^5$, $(CH_2)_nNR^5C(O)R^5$, and $(CH_2)_nNR^5SO_2R^5$; wherein heteroaryl is as defined above, and phenyl, naphthyl, and heteroaryl are optionally substituted with one to three groups independently selected from R^3 ; alkyl
20 and heterocyclyl are optionally substituted with one to three groups independently selected from R^3 and oxo; and the $(CH_2)_n$ group is optionally substituted with one to three groups independently selected from R^4 , halogen, $S(O)_pR^4$, $N(R^4)_2$, and OR^4 . In a class of this embodiment, X is selected from the group consisting of C_{1-6} alkyl, $(CH_2)_{0-1}$ -phenyl, $(CH_2)_{0-1}$ -heteroaryl, $(CH_2)_{0-1}$ -heterocyclyl, $(CH_2)_{0-1}NHC(O)R^5$,
25 $(CH_2)_{0-1}CO_2R^5$, and $(CH_2)_{0-1}C(O)N(R^5)(R^5)$; wherein phenyl and heteroaryl are optionally substituted with one to three groups independently selected from R^3 ; and alkyl and heterocyclyl are optionally substituted with one to three groups independently selected from R^3 and oxo. In a subclass of this class, heteroaryl is selected from the group consisting of pyridyl, pyrazinyl, pyrimidinyl, triazolyl, tetrazolyl, thiadiazolyl, oxadiazolyl, pyrazolyl, and imidazolyl.
30

In a fourth embodiment of compounds of formula I, Y is selected from the group consisting of C_{1-8} alkyl, C_{2-6} alkenyl, $(CH_2)C_{3-8}$ cycloalkyl, (CH_2) -phenyl, (CH_2) -naphthyl, (CH_2) -heterocyclyl, and (CH_2) -heteroaryl, wherein phenyl, naphthyl, and heteroaryl are optionally substituted with one to three groups
35 independently selected from R^3 ; and $(CH_2)_n$, alkyl, cycloalkyl, and heterocyclyl are

optionally substituted with one to three groups independently selected from R^3 and oxo. In a class of this embodiment, Y is selected from the group consisting of C₁-8 alkyl, C₂-6 alkenyl, C₅-7 cycloalkyl, and phenyl; wherein phenyl is unsubstituted or substituted with one to three groups independently selected from R^3 ; and alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R^3 and oxo. In a subclass of this class, Y is cyclohexyl or C₁-6 alkyl; wherein the cyclohexyl and alkyl groups are unsubstituted or substituted with one to three groups independently selected from R^3 and oxo.

In yet a further embodiment of compounds of structural formula I, r is 1 or 2 and s is 1.

In yet a further embodiment of the compounds of the present invention, there are provided compounds of structural formula IIa or IIb of the indicated relative stereochemical configurations having the *trans* orientation of the R^2 and piperidinecarbonyl substituents:



15

or a pharmaceutically acceptable salt thereof;
wherein

r is 1 or 2;

n is 0, 1, or 2;

20 p is 0, 1, or 2;

R^1 is hydrogen, amidino, C₁-4 alkyliminoyl, C₁-6 alkyl, C₅-6 cycloalkyl, (CH₂)₀₋₁ phenyl, (CH₂)₀₋₁ heteroaryl; wherein phenyl and heteroaryl are

unsubstituted or substituted with one to three groups independently selected from R^3 , and alkyl and cycloalkyl are unsubstituted or substituted with one to three groups

25 independently selected from R^3 and oxo;

R^2 is phenyl or thienyl optionally substituted with one to three groups independently selected from R^3 ;

- R^3 is selected from the group consisting of
- C₁₋₆ alkyl,
 - (CH₂)_n-phenyl,
 - (CH₂)_n-naphthyl,
 - 5 (CH₂)_n-heteroaryl,
 - (CH₂)_n-heterocyclyl,
 - (CH₂)_nC₃₋₇ cycloalkyl,
 - halogen,
 - OR⁴,
 - 10 (CH₂)_nN(R⁴)₂,
 - (CH₂)_nC≡N,
 - CO₂R⁴,
 - C(R⁴)(R⁴)N(R⁴)₂,
 - NO₂,
 - 15 (CH₂)_nNR⁴SO₂R⁴
 - (CH₂)_nSO₂N(R⁴)₂,
 - (CH₂)_nS(O)_pR⁴,
 - (CH₂)_nNR⁴C(O)N(R⁴)₂,
 - (CH₂)_nC(O)N(R⁴)₂,
 - 20 (CH₂)_nNR⁴C(O)R⁴,
 - (CH₂)_nNR⁴CO₂R⁴,
 - CF₃,
 - CH₂CF₃,
 - OCF₃, and
 - 25 OCH₂CF₃;

in which heteroaryl is as defined above; phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to two substituents independently selected from halogen, hydroxy, C₁₋₄ alkyl, trifluoromethyl, and C₁₋₄ alkoxy; and (CH₂)_n is unsubstituted or substituted with one to two groups

30 independently selected from halogen, hydroxy, and C₁₋₄ alkyl;

each R⁴ is independently selected from the group consisting of

- hydrogen,
- C₁₋₈ alkyl, and

C₃₋₆ cycloalkyl;

wherein cycloalkyl is unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, and C₁₋₄ alkoxy;

or two R⁴ groups together with the atom to which they are attached form a 4- to 8-

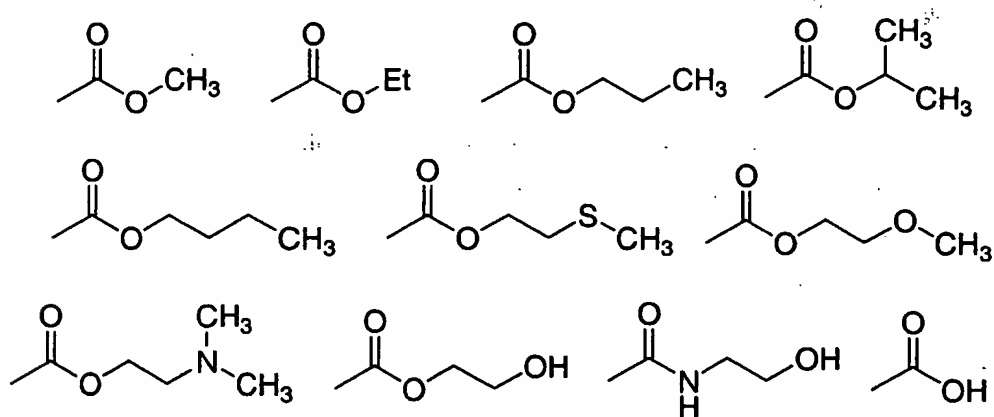
- 5 membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC₁₋₄ alkyl;

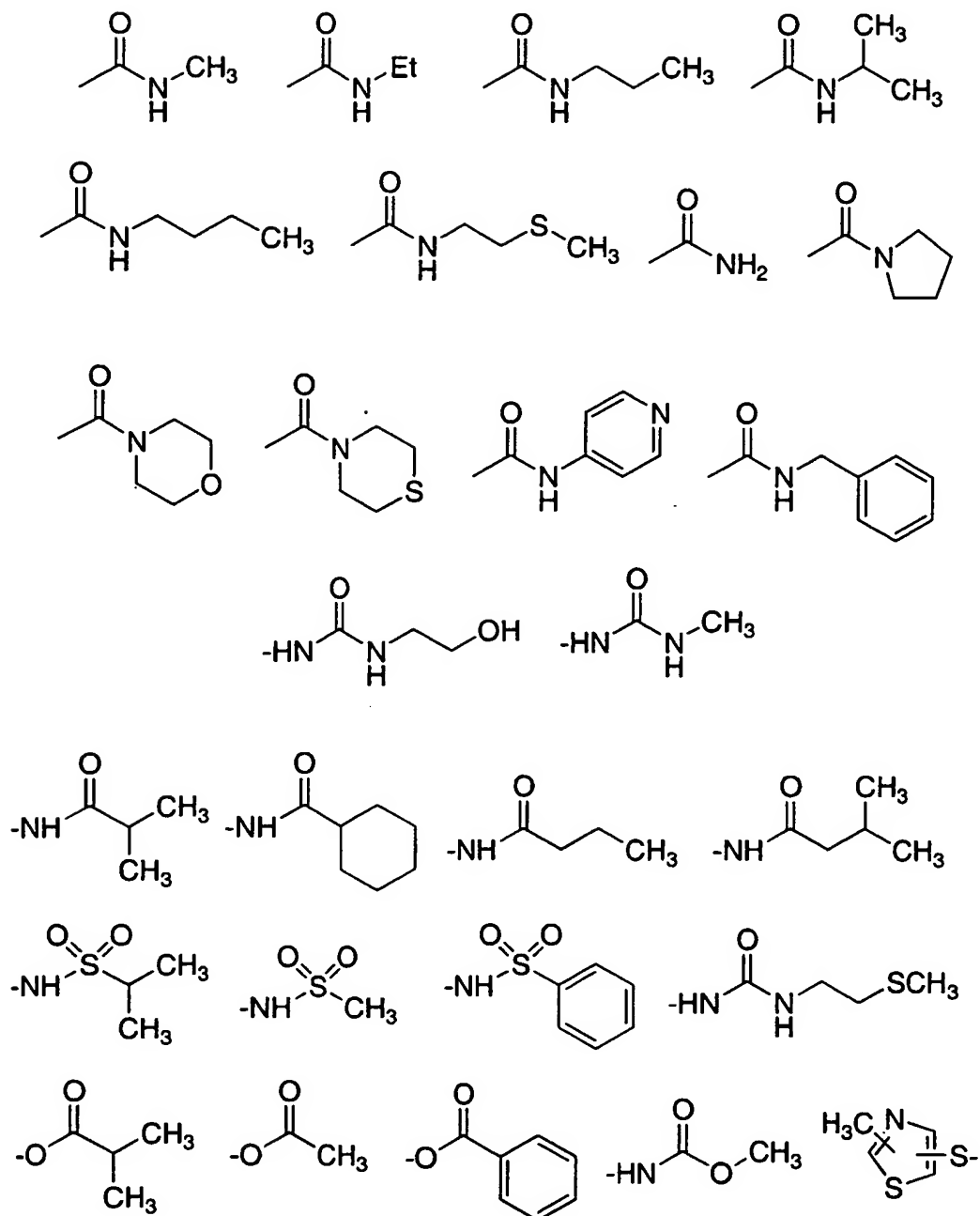
Y is selected from the group consisting of

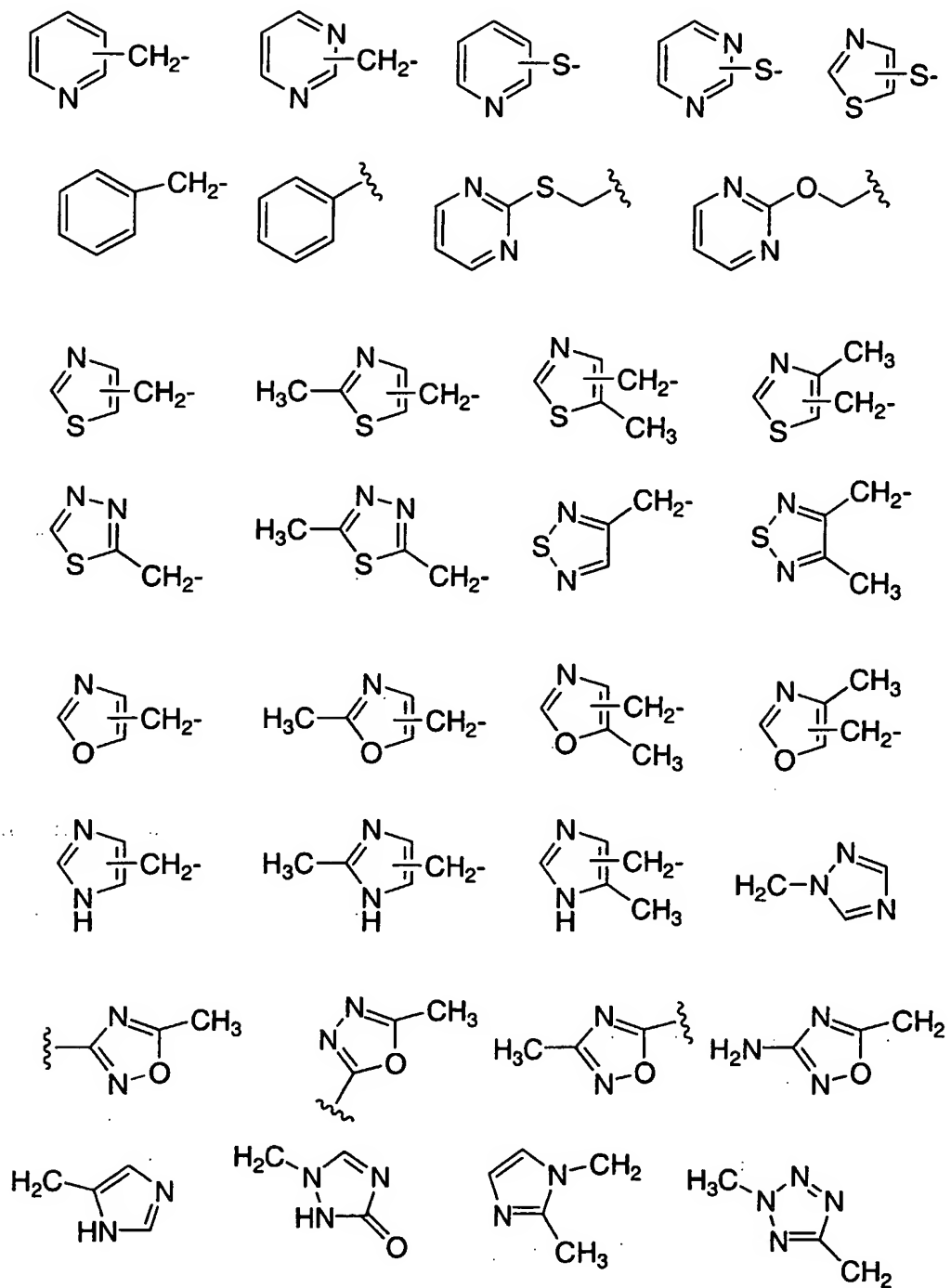
- 10 C₁₋₈ alkyl,
 C₂₋₆ alkenyl,
 (CH₂)₀₋₁C₃₋₈ cycloalkyl,
 (CH₂)₀₋₁-phenyl,
 (CH₂)₀₋₁-naphthyl, and
 (CH₂)₀₋₁-heteroaryl;

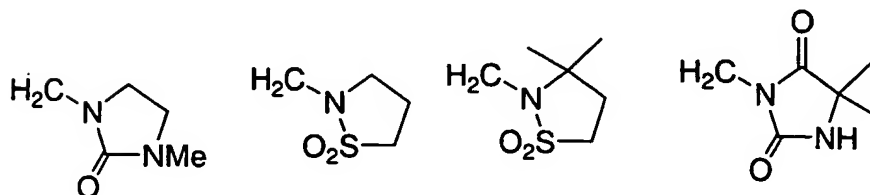
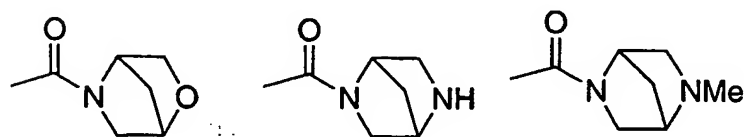
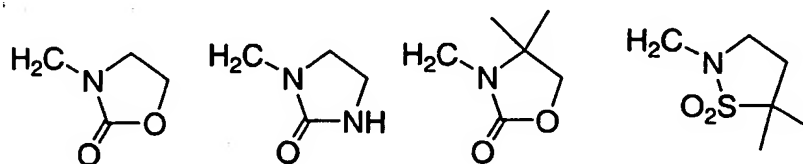
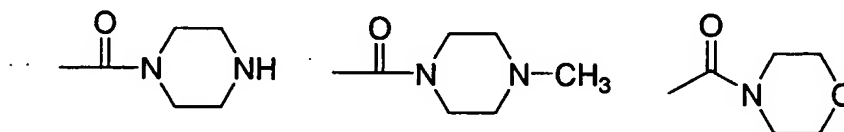
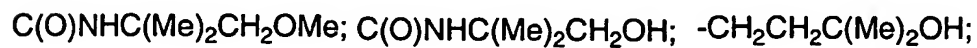
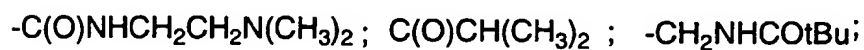
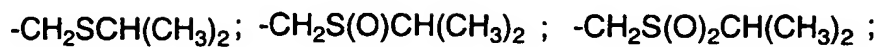
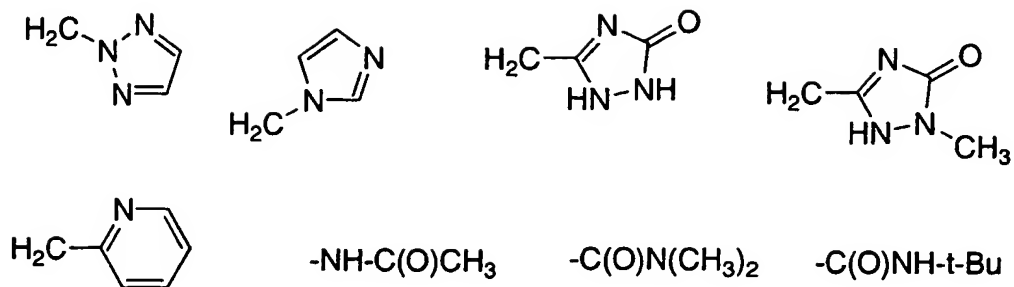
- 15 wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R³; and alkyl, (CH₂), and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R³ and oxo; and

- 20 X is selected from the group consisting of:

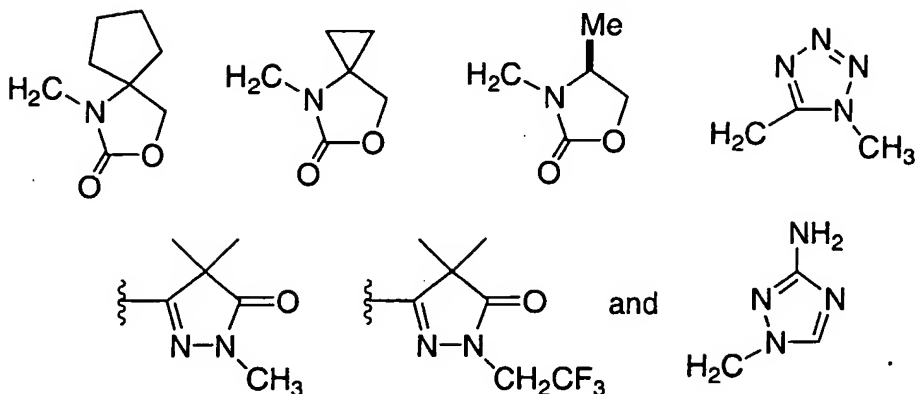




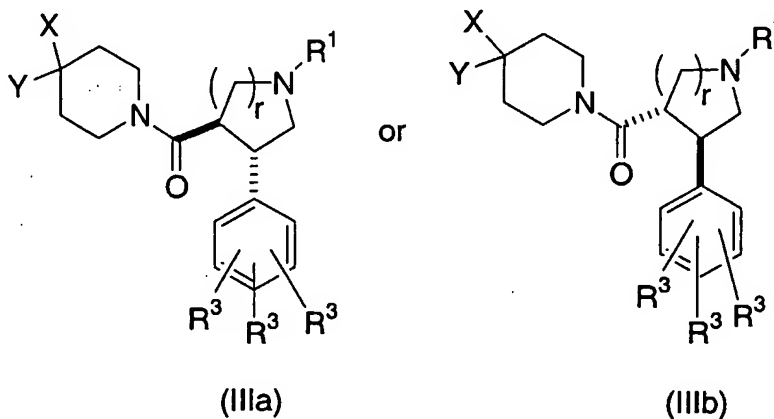




$\text{CH}_2\text{CH}_2\text{NEt}_2$; $\text{CH}_2\text{CONEt}_2$;



In yet a further embodiment of the compounds of the present invention, there are provided compounds of structural formula IIIa or IIIb of the indicated relative stereochemical configurations having the *trans* orientation of the phenyl and piperidinecarbonyl substituents:



or a pharmaceutically acceptable salt thereof;

wherein

r is 1 or 2;

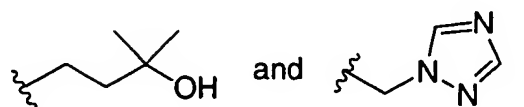
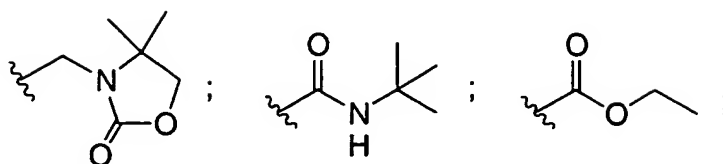
10 R^1 is hydrogen, C_{1-4} alkyl, or $(\text{CH}_2)_{0-1}$ phenyl;

each R^3 is independently selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, trifluoromethyl, and C_{1-4} alkoxy;

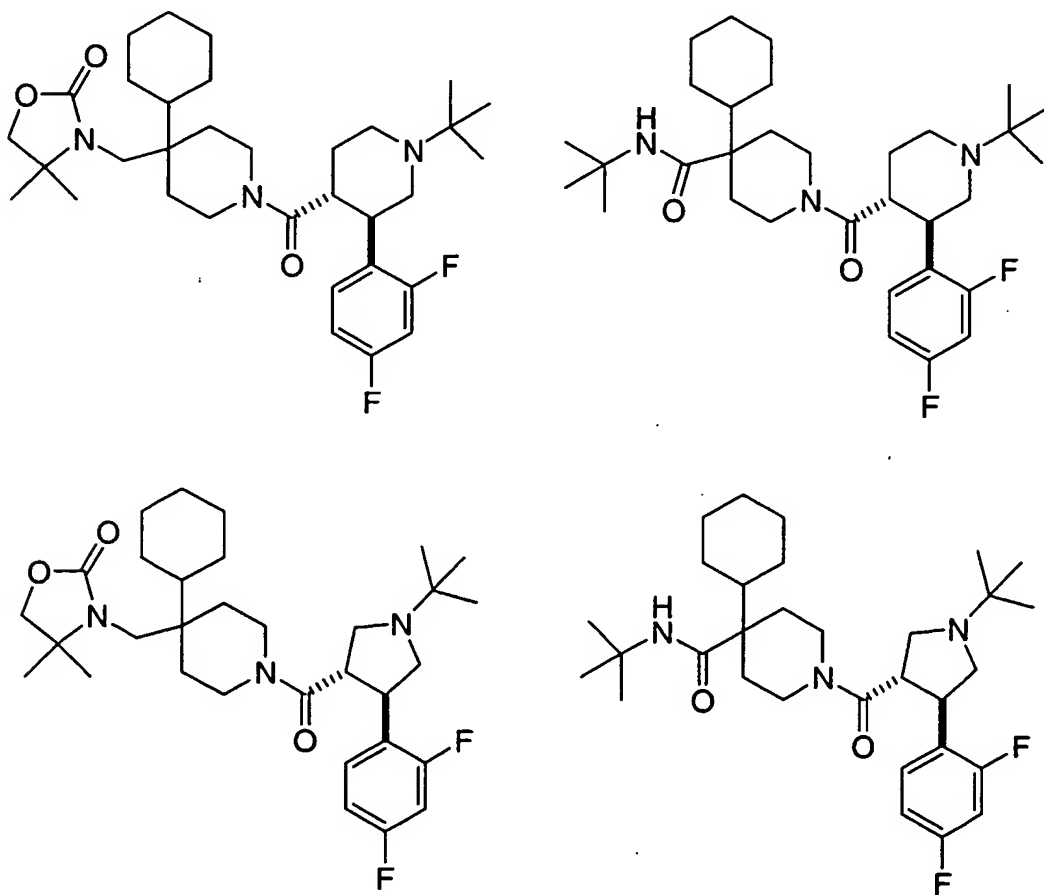
Y is cyclohexyl or phenyl; and

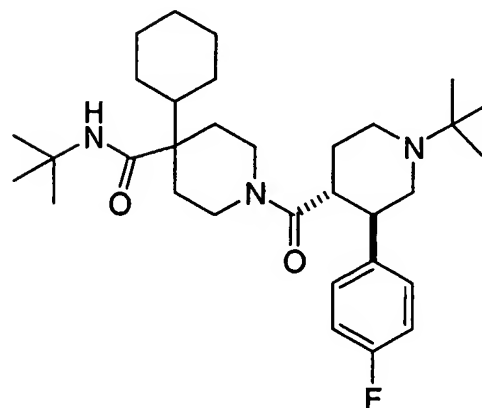
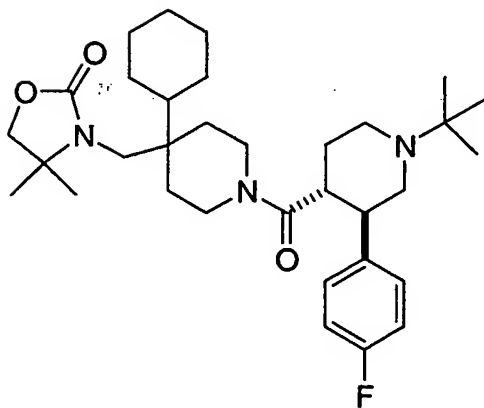
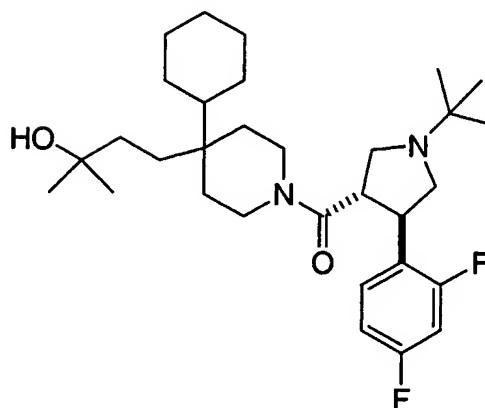
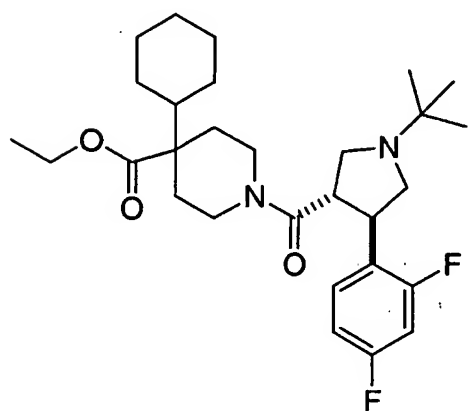
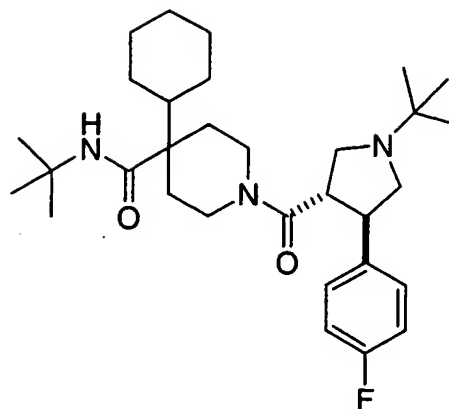
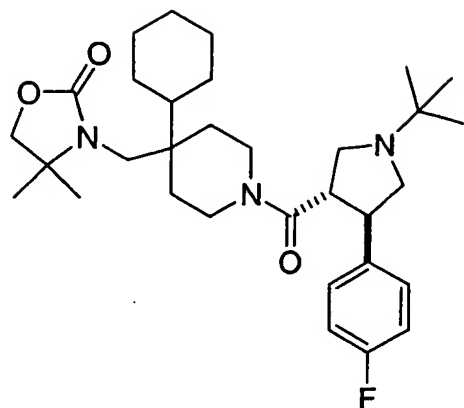
X is selected from the group consisting of

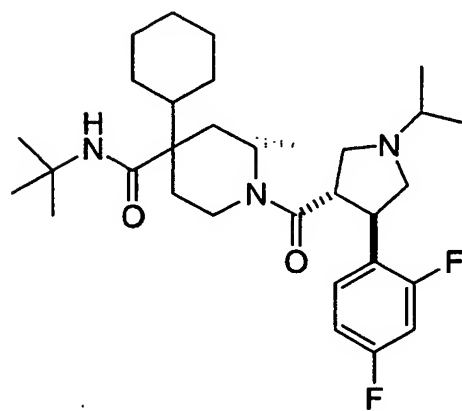
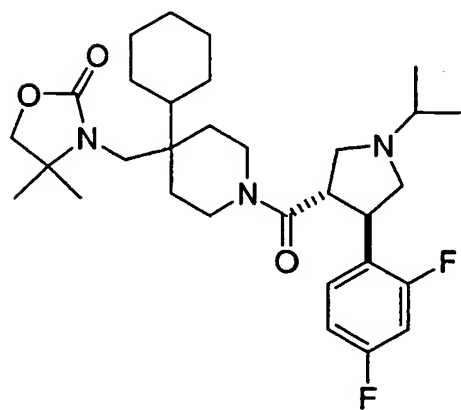
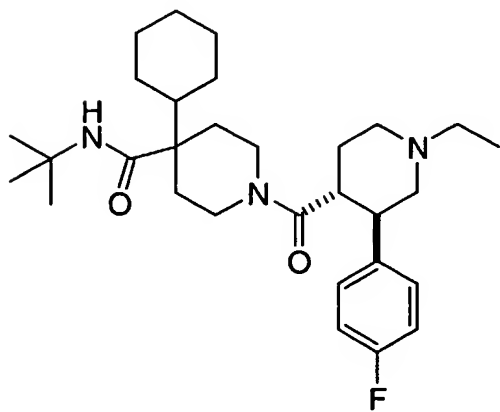
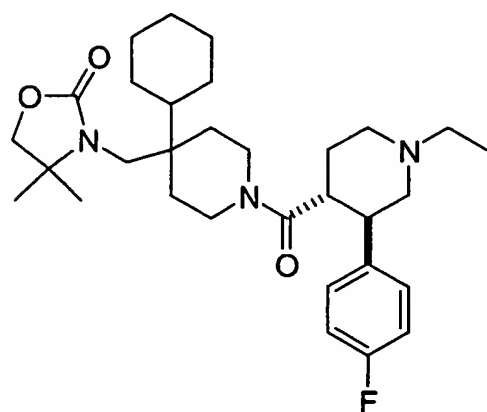
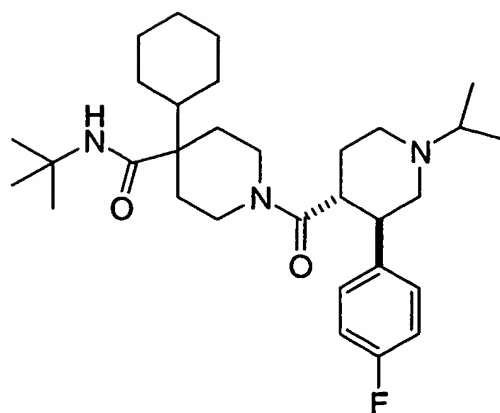
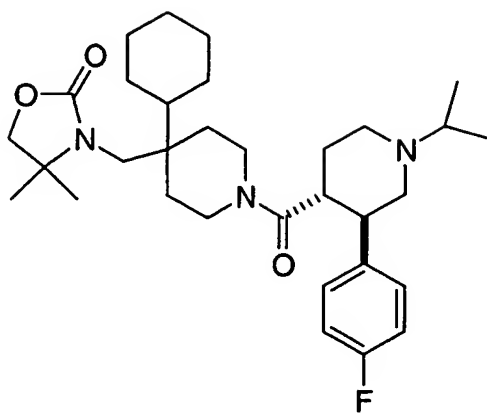
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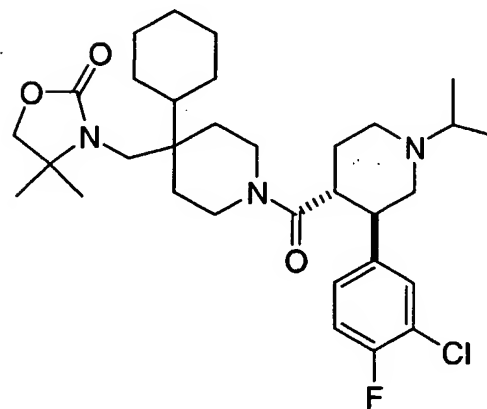
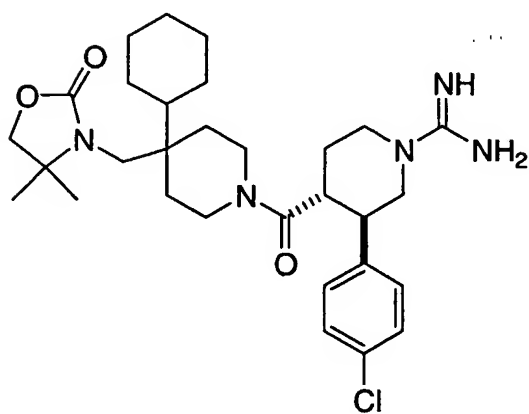
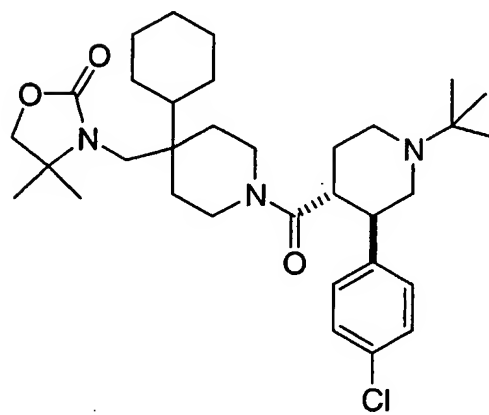
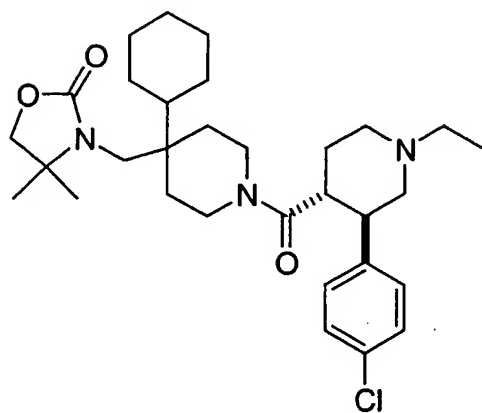
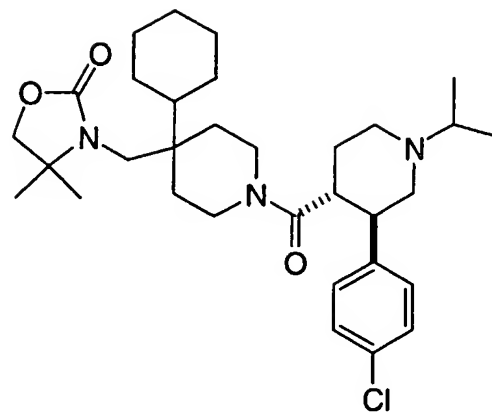
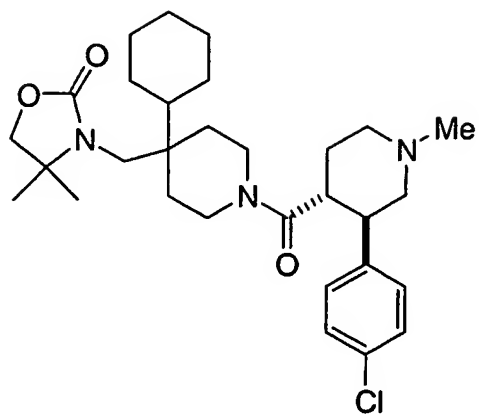
$\text{CH}_2\text{CH}_2\text{NEt}_2$; $\text{CH}_2\text{CONEt}_2$;

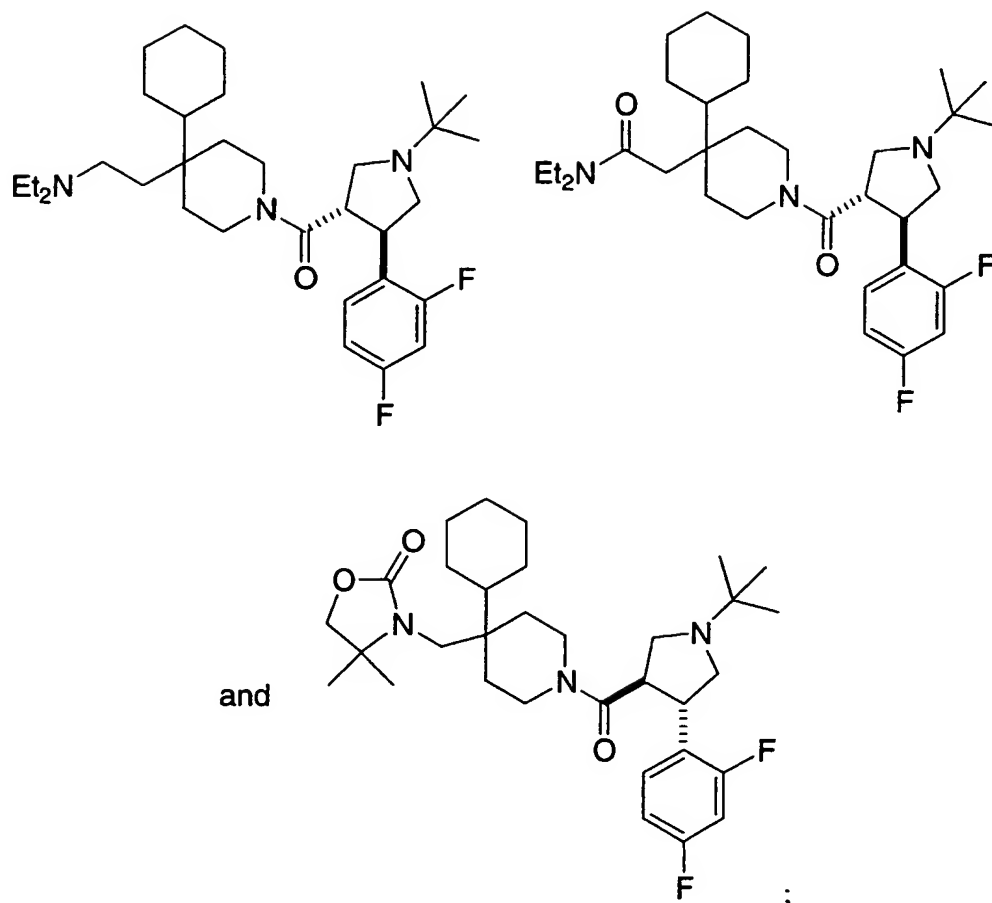
Illustrative but nonlimiting examples of compounds of the present invention that are useful as melanocortin agonists are the following:











or a pharmaceutically acceptable salt thereof.

The compounds of structural formula I are effective as melanocortin
 5 receptor agonists and are particularly effective as selective agonists of MC-4R. They
 are therefore useful for the treatment and/or prevention of disorders responsive to the
 activation of MC-4R, such as obesity, diabetes as well as male and/or female sexual
 dysfunction, in particular, erectile dysfunction, and further in particular, male erectile
 dysfunction.

10 Another aspect of the present invention provides a method for the
 treatment or prevention of obesity or diabetes in a subject in need thereof which
 comprises administering to said subject a therapeutically or prophylactically effective
 amount of a compound of structural formula I.

15 Another aspect of the present invention provides a method for the
 treatment or prevention of male or female sexual dysfunction including erectile
 dysfunction which comprises administering to a subject in need of such treatment or

prevention a therapeutically or prophylactically effective amount of a compound of structural formula I.

Another aspect of the present invention provides a pharmaceutical composition comprising a compound of structural formula I and a pharmaceutically acceptable carrier.

Yet another aspect of the present invention provides a method for the treatment or prevention of male or female sexual dysfunction including erectile dysfunction which comprises administering to a subject in need of such treatment or prevention a therapeutically or prophylactically effective amount of a compound of structural formula I in combination with a therapeutically effective amount of another agent known to be useful for the treatment of these conditions.

Yet another aspect of the present invention provides a method for the treatment or prevention of obesity which comprises administering to a subject in need of such treatment or prevention a therapeutically or prophylactically effective amount of a compound of structural formula I in combination with a therapeutically effective amount of another agent known to be useful for the treatment of this condition.

Throughout the instant application, the following terms have the indicated meanings:

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, and the like.

The term "halogen" is intended to include the halogen atoms fluorine, chlorine, bromine and iodine.

The term "C₁₋₄ alkyliminoyl" means C₁₋₃C(=NH)-.

The term "aryl" includes phenyl and naphthyl.

The term "heteroaryl" includes mono- and bicyclic aromatic rings containing from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur. "5- or 6-Membered heteroaryl" represents a monocyclic heteroaromatic ring; examples thereof include thiazole, oxazole, thiophene, furan, pyrrole, imidazole, isoxazole, pyrazole, triazole, thiadiazole, tetrazole, oxadiazole, pyridine, pyridazine, pyrimidine, pyrazine, and the like. Bicyclic heteroaromatic rings include, but are not limited to, benzothiadiazole, indole, benzothiophene, benzofuran, benzimidazole, benzisoxazole, benzothiazole, quinoline, benzotriazole, benzoxazole, isoquinoline, purine, furopyridine and thienopyridine.

The term "5- or 6-membered carbocyclyl" is intended to include non-aromatic rings containing only carbon atoms such as cyclopentyl and cyclohexyl.

The term "5 and 6-membered heterocyclyl" is intended to include non-aromatic heterocycles containing one to four heteroatoms selected from nitrogen,
5 oxygen and sulfur. Examples of a 5 or 6-membered heterocyclyl include piperidine, morpholine, thiamorpholine, pyrrolidine, imidazolidine, tetrahydrofuran, piperazine, and the like.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of
10 the other; thus for example, NR^4R^4 may represent NH_2 , $NHCH_3$, $N(CH_3)CH_2CH_3$, and the like.

An embodiment of the term "mammal in need thereof" is a "human in need thereof," said human being either male or female.

The term "composition", as in pharmaceutical composition, is intended
15 to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical
20 compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

"Erectile dysfunction" is a disorder involving the failure of a male mammal to achieve erection, ejaculation, or both. Symptoms of erectile dysfunction include an inability to achieve or maintain an erection, ejaculatory failure, premature
25 ejaculation, or inability to achieve an orgasm. An increase in erectile dysfunction is often associated with age and is generally caused by a physical disease or as a side-effect of drug treatment.

By a melanocortin receptor "agonist" is meant an endogenous or drug substance or compound that can interact with a melanocortin receptor and initiate a
30 pharmacological response characteristic of the melanocortin receptor. By a melanocortin receptor "antagonist" is meant a drug or a compound that opposes the melanocortin receptor-associated responses normally induced by another bioactive agent. The "agonistic" properties of the compounds of the present invention were

measured in the functional assay described below. The functional assay discriminates a melanocortin receptor agonist from a melanocortin receptor antagonist.

By "binding affinity" is meant the ability of a compound/drug to bind to its biological target, in the the present instance, the ability of a compound of structural formula I to bind to a melanocortin receptor. Binding affinities for the compounds of the present invention were measured in the binding assay described below and are expressed as IC₅₀'s.

"Efficacy" describes the relative intensity with which agonists vary in the response they produce even when they occupy the same number of receptors and with the same affinity. Efficacy is the property that enables drugs to produce responses. Properties of compounds/drugs can be categorized into two groups, those which cause them to associate with the receptors (binding affinity) and those that produce a stimulus (efficacy). The term "efficacy" is used to characterize the level of maximal responses induced by agonists. Not all agonists of a receptor are capable of inducing identical levels of maximal responses. Maximal response depends on the efficiency of receptor coupling, that is, from the cascade of events, which, from the binding of the drug to the receptor, leads to the desired biological effect.

The functional activities expressed as EC₅₀'s and the "agonist efficacy" for the compounds of the present invention at a particular concentration were measured in the functional assay described below.

Optical Isomers - Diastereomers - Geometric Isomers - Tautomers

Compounds of structural formula I contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of the compounds of structural formula I.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist as tautomers such as keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed within the compounds of structural formula I.

Compounds of structural formula I may be separated into their individual diastereoisomers by, for example, fractional crystallization from a suitable solvent, for example methanol or ethyl acetate or a mixture thereof, or via chiral

chromatography using an optically active stationary phase. Absolute stereochemistry may be determined by X-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

- 5 Alternatively, any stereoisomer of a compound of the general formula I, IIa, IIb, IIIa, and IIIb may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known absolute configuration.

Salts

- 10 The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly
15 preferred are the ammonium, calcium, lithium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine,
20 diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

- 25 When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, formic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, malonic, mucic, nitric,
30 pamoic, pantothenic, phosphoric, propionic, succinic, sulfuric, tartaric, p-toluenesulfonic acid, trifluoroacetic acid, and the like. Particularly preferred are citric, fumaric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

- 35 It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Utility

Compounds of formula I are melanocortin receptor agonists and as such are useful in the treatment, control or prevention of diseases, disorders or conditions responsive to the activation of one or more of the melanocortin receptors including, but are not limited to, MC-1, MC-2, MC-3, MC-4, or MC-5. Such diseases, disorders or conditions include, but are not limited to, obesity (by reducing appetite, increasing metabolic rate, reducing fat intake or reducing carbohydrate craving), diabetes mellitus (by enhancing glucose tolerance, decreasing insulin resistance), hypertension, hyperlipidemia, osteoarthritis, cancer, gall bladder disease, sleep apnea, depression, anxiety, compulsion, neuroses, insomnia/sleep disorder, substance abuse, pain, male and female sexual dysfunction (including impotence, loss of libido and erectile dysfunction), fever, inflammation, immunomodulation, rheumatoid arthritis, skin tanning, acne and other skin disorders, neuroprotective and cognitive and memory enhancement including the treatment of Alzheimer's disease. Some compounds encompassed by formula I show highly selective affinity for the melanocortin-4 receptor relative to MC-1R, MC-2R, MC-3R, and MC-5R, which makes them especially useful in the prevention and treatment of obesity, as well as male and/or female sexual dysfunction, including erectile dysfunction.

"Male sexual dysfunction" includes impotence, loss of libido, and erectile dysfunction.

"Erectile dysfunction" is a disorder involving the failure of a male mammal to achieve erection, ejaculation, or both. Symptoms of erectile dysfunction include an inability to achieve or maintain an erection, ejaculatory failure, premature ejaculation, or inability to achieve an orgasm. An increase in erectile dysfunction and sexual dysfunction can have numerous underlying causes, including but not limited to (1) aging, (b) an underlying physical dysfunction, such as trauma, surgery, and peripheral vascular disease, and (3) side-effects resulting from drug treatment, depression, and other CNS disorders.

"Female sexual dysfunction" can be seen as resulting from multiple components including dysfunction in desire, sexual arousal, sexual receptivity, and orgasm related to disturbances in the clitoris, vagina, periurethral glans, and other trigger points of sexual function. In particular, anatomic and functional modification of such trigger points may diminish the orgasmic potential in breast cancer and gynecologic cancer patients. Treatment of female sexual dysfunction with an MC-4 receptor agonist can result in improved blood flow, improved lubrication, improved

sensation, facilitation of reaching orgasm, reduction in the refractory period between orgasms, and improvements in arousal and desire. In a broader sense, "female sexual dysfunction" also incorporates sexual pain, premature labor, and dysmenorrhea.

5 Administration and Dose Ranges

Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions,
10 suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of Formula I are administered orally or topically.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage
15 may be ascertained readily by a person skilled in the art.

When treating obesity, in conjunction with diabetes and/or hyperglycemia, or alone, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.001 milligram to about 100 milligrams per kilogram of animal body weight,
20 preferably given in a single dose or in divided doses two to six times a day, or in sustained release form. In the case of a 70 kg adult human, the total daily dose will generally be from about 0.07 milligrams to about 3500 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

When treating diabetes mellitus and/or hyperglycemia, as well as other
25 diseases or disorders for which compounds of formula I are useful, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.001 milligram to about 100 milligram per kilogram of animal body weight, preferably given in a single dose or in divided doses two to six times a day, or in sustained release form. In the case of a 70 kg adult
30 human, the total daily dose will generally be from about 0.07 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

For the treatment of sexual dysfunction compounds of the present invention are given in a dose range of 0.001 milligram to about 100 milligram per
35 kilogram of body weight, preferably as a single dose orally or as a nasal spray.

Combination Therapy

Compounds of Formula I may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of Formula I are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of Formula I is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of Formula I.

Examples of other active ingredients that may be combined with a compound of Formula I for the treatment or prevention of obesity and/or diabetes, either administered separately or in the same pharmaceutical compositions, include, but are not limited to:

- (a) insulin sensitizers including (i) PPAR γ agonists such as the glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555, BRL49653 and the like), and compounds disclosed in WO97/27857, 97/28115, 97/28137 and 97/27847; (ii) biguanides such as metformin and phenformin;
- (b) insulin or insulin mimetics;
- (c) sulfonylureas, such as tolbutamide and glipizide;
- (d) α -glucosidase inhibitors (such as acarbose);
- (e) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, and other statins); (ii) sequestrants (cholestyramine, colestipol and a dialkylaminoalkyl derivatives of a cross-linked dextran), (ii) nicotiny alcohol nicotinic acid or a salt thereof, (iii) proliferator-activator receptor α agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and benzaifibrate), (iv) inhibitors of cholesterol absorption for example beta-sitosterol and (acyl CoA:cholesterol acyltransferase) inhibitors for example melinamide, (v) probucol, (vi) vitamin E, and (vii) thymomimetics;
- (f) PPAR δ agonists, such as those disclosed in WO97/28149;
- (g) anti-obesity serotonergic agents, such as fenfluramine, dexfenfluramine, phentermine, and sibutramine;
- (h) β 3-adrenoreceptor agonists;

- (i) pancreatic lipase inhibitors, such as orlistat;
- (j) feeding behavior modifying agents, such as neuropeptide Y Y1 and Y5 antagonists, such as those disclosed in WO 97/19682, WO 97/20820, WO 97/20821, WO 97/20822, WO 97/20823, WO 01/14376, and U.S. Patent No. 6,191,160;
- (k) orexin-1 receptor antagonists;
- (l) PPAR α agonists such as described in WO 97/36579 by Glaxo;
- (m) PPAR γ antagonists as described in WO97/10813;
- (n) serotonin reuptake inhibitors such as fluoxetine, paroxetine, and sertraline;
- (o) growth hormone secretagogues, such as MK-0677;
- (p) cannabinoid receptor ligands, such as cannabinoid CB₁ receptor antagonists or inverse agonists; and
- (q) protein tyrosine phosphatase-1B (PTP-1B) inhibitors.
- Examples of anti-obesity agents that can be employed in combination with a compound of Formula I are disclosed in "Patent focus on new anti-obesity agents," Exp. Opin. Ther. Patents, 10: 819-831 (2000); "Novel anti-obesity drugs," Exp. Opin. Invest. Drugs, 9: 1317-1326 (2000); and "Recent advances in feeding suppressing agents: potential therapeutic strategy for the treatment of obesity," Exp. Opin. Ther. Patents, 11: 1677-1692 (2001). The role of neuropeptide Y in obesity is discussed in Exp. Opin. Invest. Drugs, 9: 1327-1346 (2000). Cannabinoid receptor ligands are discussed in Exp. Opin. Invest. Drugs, 9: 1553-1571 (2000).
- Examples of other active ingredients that may be combined with a compound of Formula I for the treatment or prevention of male or female sexual dysfunction, in particular, male erectile dysfunction, either administered separately or in the same pharmaceutical compositions, include, but are not limited to (a) type V cyclic-GMP-specific phosphodiesterase (PDE-V) inhibitors, including sildenafil and (6R, 12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (IC-351); (b) alpha-adrenergic receptor antagonists, including phentolamine and yohimbine or pharmaceutically acceptable salts thereof; (c) dopamine receptor agonists, such as apomorphine or pharmaceutically acceptable salts thereof; and (d) nitric oxide (NO) donors.

Pharmaceutical Compositions

Another aspect of the present invention provides pharmaceutical compositions which comprises a compound of Formula I and a pharmaceutically acceptable carrier. The pharmaceutical compositions of the present invention
5 comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

10 The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient.
15 They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide
20 variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions,
25 elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

30 Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound
35 in these compositions may, of course, be varied and may conveniently be between

about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

5 The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to
10 materials of the above type, a liquid carrier such as a fatty oil.

 Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and
15 a flavoring such as cherry or orange flavor.

 Compounds of formula I may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under
20 ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

 The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must
25 be sterile and must be fluid to the extent that easy-syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures
30 thereof, and vegetable oils.

Preparation of Compounds of the Invention

 The compounds of structural formula I of the present invention can be prepared according to the procedures of the following Schemes and Examples, using
35 appropriate materials and are further exemplified by the following specific examples.

Moreover, by utilizing the procedures described in detail in PCT International Application Publications WO 99/64002 (16 December 1999) and WO 00/74679 (14 December 2000), which are incorporated by reference herein in their entirety, in conjunction with the disclosure contained herein, one of ordinary skill in the art can

5 readily prepare additional compounds of the present invention claimed herein. The compounds illustrated in the examples are not, however, to be construed as forming the only genus that is considered as the invention. The Examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes

10 of the following preparative procedures can be used to prepare these compounds. The instant compounds are generally isolated in the form of their pharmaceutically acceptable salts, such as those described previously hereinabove. The free amine bases corresponding to the isolated salts can be generated by neutralization with a suitable base, such as aqueous sodium hydrogencarbonate, sodium carbonate, sodium

15 hydroxide, and potassium hydroxide, and extraction of the liberated amine free base into an organic solvent followed by evaporation. The amine free base isolated in this manner can be further converted into another pharmaceutically acceptable salt by dissolution in an organic solvent followed by addition of the appropriate acid and subsequent evaporation, precipitation, or crystallization. All temperatures are degrees

20 Celsius unless otherwise noted. Mass spectra (MS) were measured by electron-spray ion-mass spectroscopy.

The phrase "standard peptide coupling reaction conditions" means coupling a carboxylic acid with an amine using an acid activating agent such as EDC, DCC, and BOP in an inert solvent such as methylene chloride in the presence of a

25 catalyst such as HOBT. The use of protecting groups for the amine and carboxylic acid functionalities to facilitate the desired reaction and minimize undesired reactions is well documented. Conditions required to remove protecting groups are found in standard textbooks such as Greene, T, and Wuts, P. G. M., *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, NY, 1991. CBZ and BOC

30 are commonly used protecting groups in organic synthesis, and their removal conditions are known to those skilled in the art. For example, CBZ may be removed by catalytic hydrogenation in the presence of a noble metal or its oxide such as palladium on activated carbon in a protic solvent such as methanol or ethanol. In cases where catalytic hydrogenation is contraindicated due to the presence of other

35 potentially reactive functionalities, removal of CBZ groups can also be achieved by

treatment with a solution of hydrogen bromide in acetic acid or by treatment with a mixture of TFA and dimethylsulfide. Removal of BOC protecting groups is carried out with a strong acid, such as trifluoroacetic acid, hydrochloric acid, or hydrogen chloride gas, in a solvent such as methylene chloride, methanol, or ethyl acetate.

5

Abbreviations Used in the Description of the Preparation of the Compounds of the Present Invention:

BOC (boc)	t-butyloxycarbonyl
BOP	benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
Bu	butyl
calc.	calculated
CBZ (Cbz)	benzyloxycarbonyl
c-hex	cyclohexyl
c-pen	cyclopentyl
c-pro	cyclopropyl
DEAD	diethyl azodicarboxylate
DIEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
EDC	1-(3-dimethylaminopropyl)3-ethylcarbodiimide HCl
eq.	equivalent(s)
ES-MS	electron spray ion-mass spectroscopy
Et	ethyl
EtOAc	ethyl acetate
HATU	N-[(dimethylamino)-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i>] pyridin-1-ylmethylene]- <i>N</i> -methylmethanaminium hexafluorophosphate N-oxide
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole hydrate
HPLC	high performance liquid chromatography
LDA	lithium diisopropylamide
MC- <i>x</i> R	melanocortin receptor (<i>x</i> being a number)
Me	methyl

MF	molecular formula
MS	mass spectrum
Ms	methanesulfonyl
OTf	trifluoromethanesulfonyl
Ph	phenyl
Phe	phenylalanine
Pr	propyl
prep.	prepared
PyBrop	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
r.t.	room temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography.

Reaction Schemes A-L illustrate the methods employed in the synthesis of the compounds of the present invention of structural formula I. All substituents are as defined above unless indicated otherwise.

- 5 Reaction Scheme A illustrates a key step in the synthesis of the novel compounds of structural formula I of the present invention. As shown in reaction Scheme A, the reaction of a 4-substituted piperidine of 1 with a carboxylic acid derivative of formula 2 affords a title compound of structural formula I where R¹ is an *N-tert*-butoxycarbonyl group (*N*-BOC). The amide bond coupling reaction illustrated
- 10 in reaction Scheme A is conducted in an appropriate inert solvent such as methylene chloride, dimethylformamide (DMF) or the like and may be performed with a variety of reagents suitable for amide coupling reactions such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) or benzotriazol-1-
- 15 yloxytripyrrolidinephosphonium hexafluorophosphate (PyBOP). Preferred conditions for the amide bond coupling reaction shown in reaction Scheme A are known to those skilled in organic synthesis. Such modifications may include, but are not limited to, the use of basic reagents such as triethylamine (TEA) or *N*-methylmorpholine (NMM), or the addition of an additive such as 1-hydroxybenzotriazole (HOBt). Alternatively, 4-substituted piperidines of formula 1 may be treated with an active
- 20 ester or acid chloride derived from carboxylic acid 2 which also affords compounds of

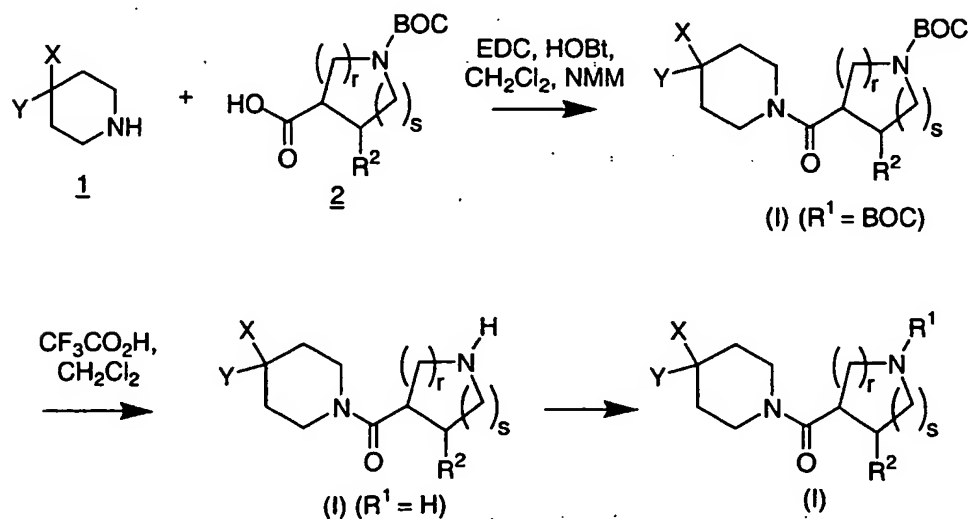
structural formula I ($R^1 = \text{BOC}$). The amide bond coupling shown in reaction Scheme A is usually conducted at temperatures between 0°C and room temperature, occasionally at elevated temperatures, and the coupling reaction is typically conducted for periods of 1 to 24 hours.

5 If it is desired to produce a compound of structural formula I wherein R^1 is a hydrogen, the *N*-BOC protected compounds of structural formula I are then deprotected under acidic conditions, for instance using trifluoroacetic acid in a solvent like methylene chloride at room temperature.

10 When it is desired to prepare compounds of structural formula I wherein R^1 is not a hydrogen, the compounds of general formula I ($R^1 = \text{H}$) may be further modified using the methodology described below in reaction Scheme L.

Reaction Schemes B-I illustrate methods for the synthesis of the carboxylic acids of general formula 2 that are utilized in the amide bond coupling reaction shown in reaction Scheme A. Reaction Schemes J-K illustrate additional
 15 methods for the synthesis of 4-substituted piperidines of general formula 1 that are used in that same step. The compounds of structural formula I in which the R^1 substituent is a group other than a hydrogen atom are generally prepared from compounds of structural formula I wherein $R = \text{H}$ using a variety of synthetic methods known in the literature of organic synthesis. Specific examples of such
 20 transformations are outlined in reaction Schemes and provided in the procedures for the Examples presented below.

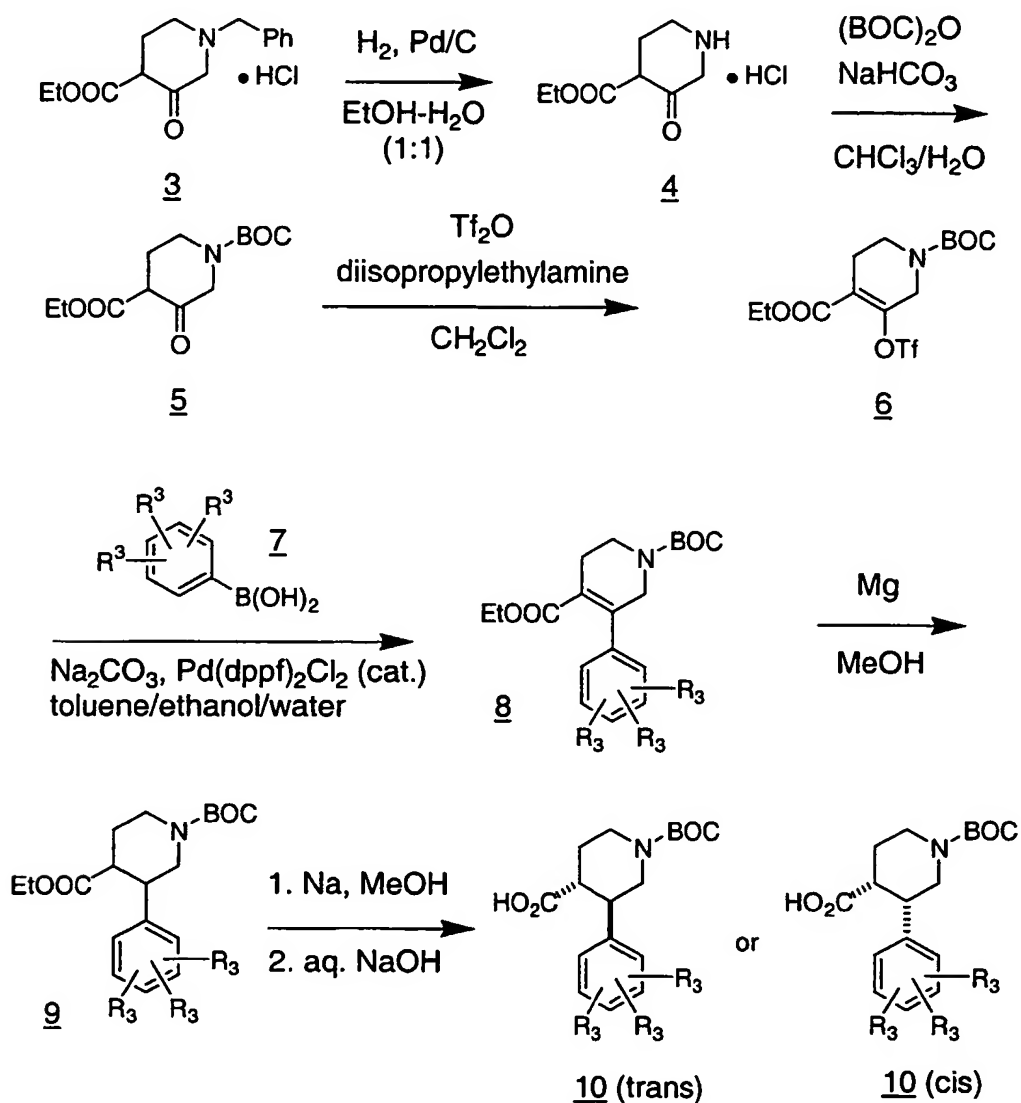
Scheme A



Reaction Scheme B illustrates a preferred method for the synthesis of compounds of general formula 2 wherein *r* is 2 and *s* is 1 such that the resulting heterocycle is a 3-aryl-4-piperidine carboxylic acid derivative 10. The synthesis of 10 begins with a commercially available β -keto ester such as 3. Generally a protecting group interchange of an *N*-BOC group for the *N*-benzyl group is performed initially. Thus a β -keto ester of formula 3 is subjected to debenzylation by hydrogenolysis using a palladium-on-carbon catalyst in a solvent system such as 1:1 ethanol-water under a hydrogen atmosphere. The resulting piperidone 4 is then protected as its *tert*-butyl carbamate using BOC anhydride in the presence of a base and a suitable solvent. For example, this can be accomplished in a two phase mixture of chloroform and aqueous sodium bicarbonate as shown. Incorporation of the 3-aryl substituent is then performed in two steps. First, the β -keto ester group is converted to the corresponding vinyl triflate 6 using trifluoromethanesulfonic anhydride and an organic base like *N,N*-diisopropylethylamine in an aprotic solvent such as methylene chloride. The resulting vinyl triflate 6 is then subjected to a palladium-catalyzed cross-coupling reaction with an aryl boronic acid (7) using a palladium (II) catalyst such as [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II). Preferred conditions for this reaction are the use of a toluene-ethanol-aqueous sodium carbonate solvent system at an elevated temperature, for instance 50-100°C, for a period of 2-24 hours. The resulting aryl-substituted tetrahydropyridine derivative 8 can be reduced to a piperidine such as 9 using a variety of known techniques and the method chosen will determine the stereochemical outcome of the product. For instance, hydrogenation of 8 with a palladium on carbon catalyst in a solvent such as ethanol affords *cis*-3,4-disubstituted piperidines of general formula 9. Alternatively, a dissolving metal reduction using a metal, such as magnesium in methanol, reduces the double bond of 8 and produces a mixture of both *cis* and *trans* 3,4-disubstituted piperidines of formula 9. The resulting mixture of *cis* and *trans* diastereoisomers may be separated chromatographically or it may be subsequently epimerized to afford the pure *trans* isomer of 9 by treating the mixture with a base like sodium methoxide in methanol. Finally, hydrolysis of either the *cis* or *trans* 3-aryl-4-piperidine carboxylic ester 9 affords either a *cis* or *trans* 3-aryl-4-piperidine carboxylic acid of general formula 10, corresponding to an acid of general formula 2 wherein *r* is 2 and *s* is 1. The *cis* or *trans* carboxylic acids of general formula 10 are produced as racemates and either may be resolved to afford enantiomerically pure compounds by methods known in organic synthesis. Preferred methods include resolution by crystallization of

diastereoisomeric salts derived from acids 10 and a chiral amine base or the use of chiral stationary phase liquid chromatography columns.

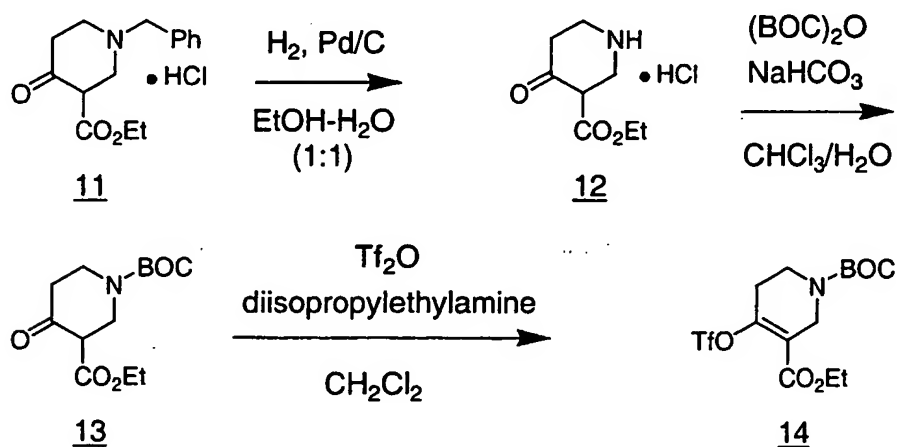
Scheme B

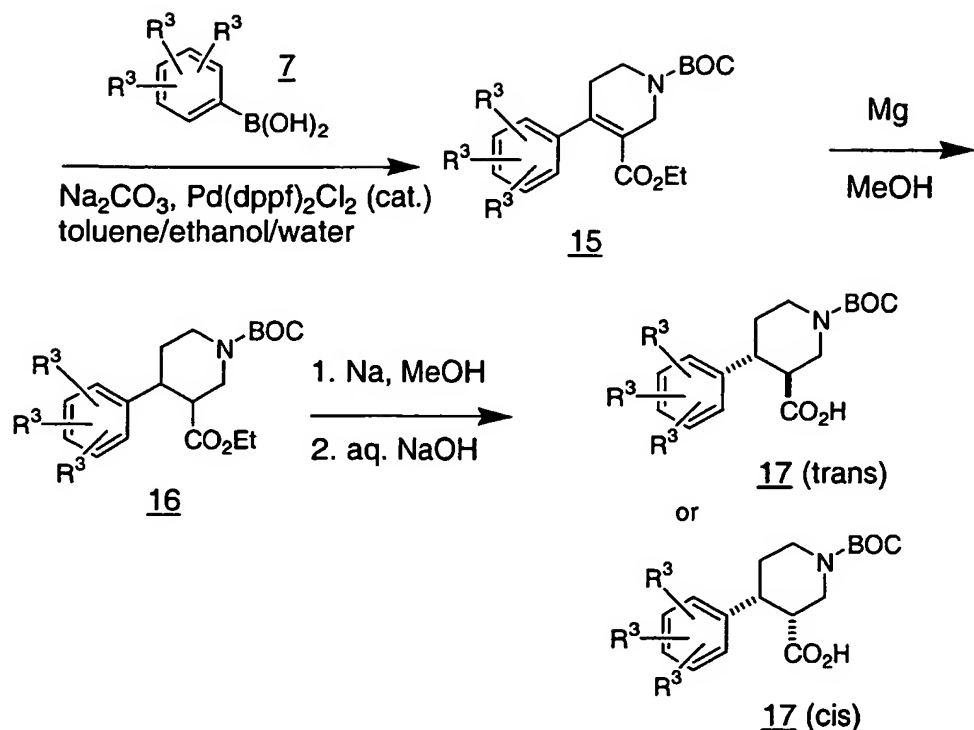


5 Reaction Scheme C illustrates a preferred method for the synthesis of compounds of general formula 2 wherein *r* is 1 and *s* is 2, such that the resulting heterocycle is a 4-aryl-3-piperidine-carboxylic acid derivative 17. The synthesis of 17 is similar to the one shown in reaction Scheme B, and may begin with either of the commercially available β -keto esters 11 or 12. Conversion of one of these starting

- materials to the *N*-BOC-protected piperidine 13 is performed as shown and the resulting β -keto ester is subjected to the two-step arylation protocol previously described to yield 15. Reduction of the double bond of 15 using conditions appropriate for obtaining either *cis* or *trans* 17 is followed by ester hydrolysis which
- 5 affords either a *cis* or *trans* 4-aryl-3-piperidine-carboxylic acid of general formula 17 which corresponds to an acid of general formula 2 wherein *r* is 1 and *s* is 2. The *cis* or *trans* carboxylic acids of general formula 17 are produced as racemates and either may be resolved to afford enantiomerically pure compounds by methods known in organic synthesis. Preferred methods include resolution by crystallization of
- 10 diastereoisomeric salts derived from the acids 17 and a chiral amine base or by the use of chiral stationary phase liquid chromatography columns.

Scheme C

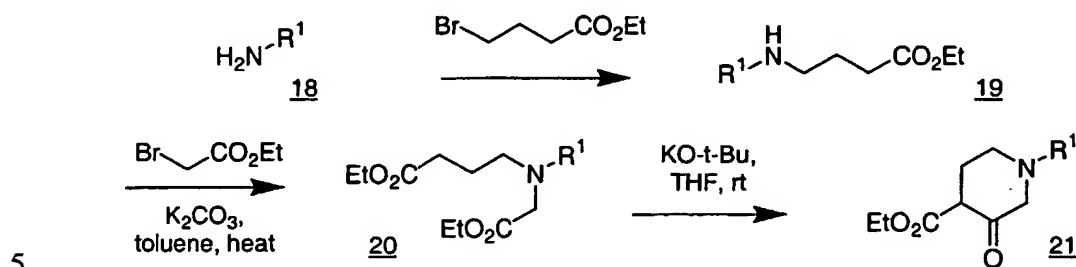




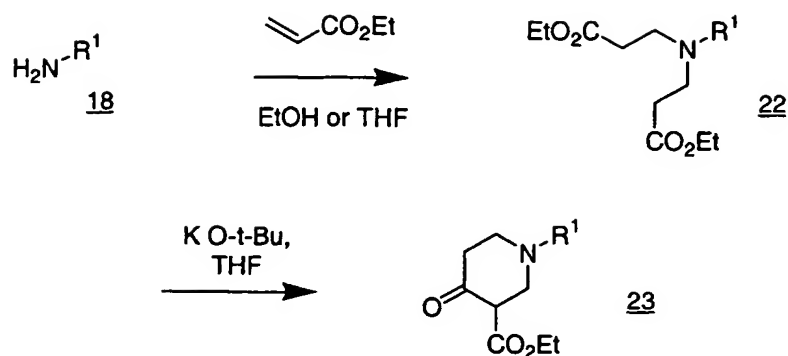
- The synthesis of the *N*-BOC protected carboxylic acids of general formula **10** and **17** illustrated in reaction Schemes B and C are useful for the preparation of title compounds of structural formula I bearing a variety of R^1 substituents as noted above. For the synthesis of certain title compounds of structural formula I, for instance when it is desired that R^1 be a *tert*-butyl group, it is preferable to incorporate that R^1 substituent at an earlier stage of the synthesis. The synthesis of a 1-substituted-3-ketopiperidine-4-carboxylic ester (**21**) is shown in reaction Scheme D. A primary amine **18** bearing a desired R^1 substituent like a *tert*-butyl group is
- 5 reacted with ethyl 4-bromobutyrate at elevated temperature in the absence of a solvent to afford the *N*-substituted ethyl 4-aminobutyrate **19**. The amino ester **19** is then alkylated a second time with ethyl bromoacetate in a high boiling inert solvent such as toluene and in the presence of a base such as powdered potassium carbonate. The resulting aminodiester of general formula **20** are then cyclized using an
- 10 intramolecular Dieckmann reaction to afford piperidines such as **21**. The Dieckmann reaction is performed using a strong base such as potassium *tert*-butoxide or the like, in an aprotic solvent such as THF at temperatures between room temperature and the boiling point of the solvent. The resulting 1-substituted-3-ketopiperidine-4-carboxylic ester **21** corresponds to a compound of general formula **5** shown in

reaction Scheme B, where the BOC group is replaced with the desired R^1 substituent. The compounds of general formula 21 may then be converted to compounds of general formula 2 where the R^1 substituent replaces the BOC group using the reaction sequence illustrated in reaction Scheme B.

Scheme D



When it is desirable to synthesize a compound of general formula 17 wherein the BOC group is replaced with a substituent group R^1 , a reaction sequence similar to the one illustrated in reaction Scheme C may be employed as shown in reaction Scheme E. An amine 18 bearing the desired R^1 substituent is first subjected to a Michael addition with excess ethyl acrylate in the presence of a solvent such as THF or ethanol. The resulting diester 22 is then converted to a 1-substituted-4-ketopiperidine-3-carboxylic ester 23 using an intramolecular Dieckmann reaction under conditions similar to those illustrated in reaction Scheme C. The substituted piperidine 23 corresponds to a compound of general formula 13 shown in reaction Scheme C, wherein the BOC group is replaced with the desired R^1 substituent. The compounds of general formula 23 may then be converted to compounds of general formula 2 where the R^1 substituent replaces the BOC group using the methodology illustrated in reaction Scheme C.

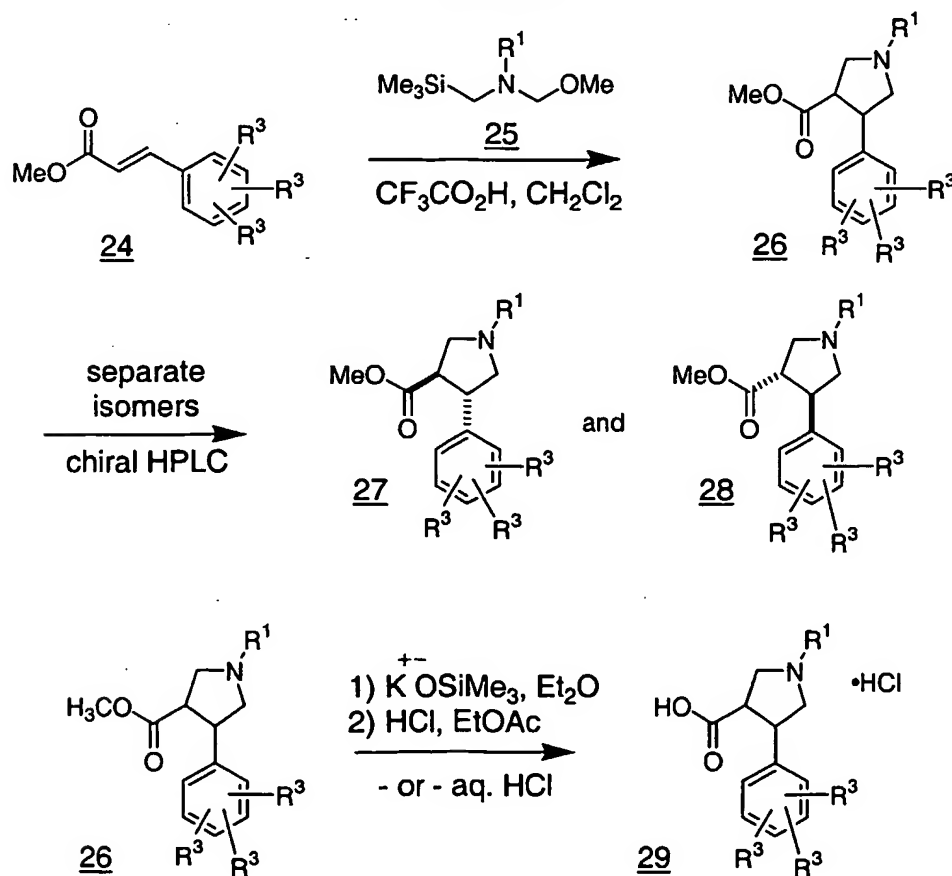
Scheme E

Reaction Scheme F illustrates a strategy for the synthesis of compounds of general formula 2 when the values of *r* and *s* are selected such that the resulting heterocycle is a 3-aryl-4-pyrrolidine carboxylic acid derivative (29). The preferred method for the synthesis of compounds of general formula 29 involves the azomethine ylid 3+2 cycloaddition reaction of an azomethine ylid precursor of general formula 25 and a substituted cinnamic ester 24. The azomethine cycloaddition reaction of 24 and 25 affords the 3,4-disubstituted pyrrolidine 26, and the stereochemical relationship of the substituents on the newly formed pyrrolidine ring is determined by the stereochemistry of the double bond in the cinnamate ester 24. Thus the *trans* ester 24 affords a *trans* 3,4-disubstituted pyrrolidine of formula 26 as shown. The corresponding *cis* cinnamate ester affords a *cis* 3,4-disubstituted pyrrolidine of general formula 26. *Cis* or *trans* 3-arylpyrrolidine-4-carboxylic esters of general formula 26 may be resolved to afford enantiomerically pure compounds using a method such as resolution by crystallization of the diastereoisomeric salts derived from 26 and a chiral carboxylic acid, or directly by the use of chiral stationary phase liquid chromatography columns. Reaction Scheme F illustrates the case where a *trans* cinnamic ester 24 is converted to a *trans* 3,4-disubstituted pyrrolidine 26 and its subsequent resolution affords the enantiomerically pure *trans* pyrrolidine esters 27 and 28. Finally, the esters of general formula 26 (or their pure enantiomers 27 and 28) are hydrolyzed to the corresponding amino acid hydrochlorides of general formula 29 as shown at the bottom of reaction Scheme F.

Amino acids of general formula 29 are zwitterionic. Therefore it is in some cases difficult to achieve efficient separation and purification of these compounds from aqueous reactions or workups. In these cases it is preferred to effect

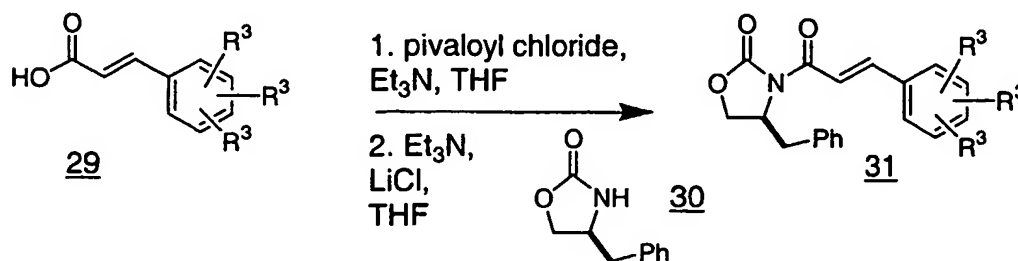
- the hydrolysis using a reagent such potassium trimethylsilanolate in diethyl ether. Under these conditions the potassium salt of the carboxylic acid is produced which affords an easily isolated precipitate in ether. The resulting salt is then converted to the corresponding amino acid hydrochloride by treatment with excess hydrochloric acid in a suitable solvent such as ethyl acetate. Alternatively, esters such as 26 may be converted directly to the amino acid hydrochlorides 29 under acidic hydrolysis conditions. The hydrolysis of the ester 26 is achieved by prolonged reaction with concentrated hydrochloric acid at an elevated temperature. For example, this reaction may be conducted in 8 M hydrochloric acid at reflux overnight. The reaction mixture is then cooled and evaporated *in vacuo* to afford the amino acid hydrochloride 29. The amino acid hydrochlorides of general formula 29 correspond to an amino acid hydrochloride of general formula 2 wherein both *r* and *s* are 1 and may be employed directly in the amide bond coupling step illustrated in reaction Scheme A to produce the compounds of the present invention of structural formula I.

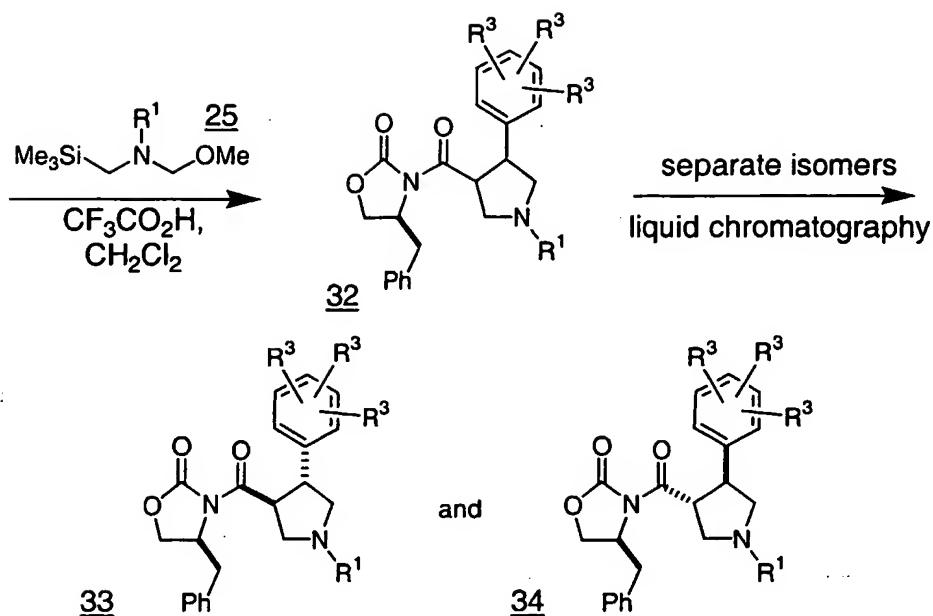
Scheme F



Another preferred method for the synthesis of enantiomerically pure 3-arylpyrrolidine-4-carboxylic acid derivatives is illustrated in reaction Scheme G. In this synthetic method, a substituted cinnamic acid of general formula 29 is first derivatized with a chiral auxiliary such as (*S*)-(-)-4-benzyl-2-oxazolidinone (30). The acylation of chiral auxiliary 30 with cinnamic acids of formula 29 is performed by initial activation of the acid to afford a mixed anhydride. Typically acids of general formula 29 are reacted with an acid chloride such as pivaloyl chloride in the presence of a base such as triethylamine and in a suitable aprotic solvent such as THF. The intermediate cinnamyl-pivaloyl anhydride is converted to the product 31 by reaction with the oxazolidinone 30 in the presence of lithium chloride, an amine base such as triethylamine and in a solvent such as THF, and the reaction is conducted at temperatures between -20°C and room temperature for periods of 1-24 hours. Alternatively, the oxazolidinone 30 may be deprotonated with a strong base such as *n*-butyllithium in THF at low temperatures such as -78°C and then reacted with a mixed anhydride obtained from acid 29 and an acid chloride like pivaloyl chloride as noted above. The cinnamyl oxazolidinone of general formula 31, which is produced by either of these methods, is then reacted with the azomethine ylid precursor 25 in a manner similar to that described in reaction Scheme F, and the products of the reaction are the substituted pyrrolidines of general formulas 33 and 34 as shown. The products 33 and 34 are diastereoisomers of each other and may therefore be separated by standard methods such as recrystallization or by liquid chromatography on a solid support such as silica gel. As discussed above, if the *cis* isomer of the cinnamic acid of general formula 29 is employed in the first step of reaction Scheme G, then a *cis* isomer of the substituted cinnamyl oxazolidinone 31 is produced. If such a *cis* cinnamyl oxazolidinone is then subjected to the azomethine ylid cycloaddition with an azomethine ylid precursor of formula 25, the products are the diastereoisomeric *cis*-disubstituted pyrrolidines related to 33 and 34.

Scheme G



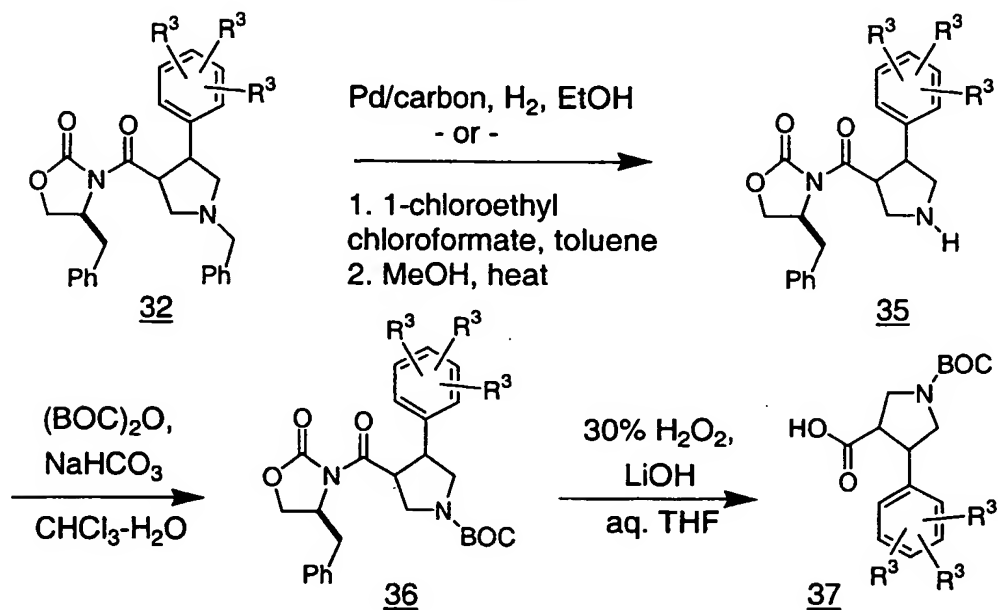


- The azomethine ylid cycloaddition reactions shown in reaction Schemes F and G are generally conducted with the commercially available azomethine ylid precursor *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)-benzylamine (**25**, $\text{R}^1 = -\text{CH}_2\text{Ph}$). When the R^1 substituent in the title compounds of structural formula I is chosen to be a group other than benzyl, it is generally preferable to remove the benzyl group from the substituted pyrrolidine compound at this point, and replace it with a more readily removed protecting group such as an *N*-BOC group. Reaction Scheme H illustrates this process with a generalized 3,4-disubstituted pyrrolidine of formula **32**. The preferred method for removal of the *N*-benzyl group from compounds of general formula **32** will depend upon the identity of the R^3 substituents. If these substituents are unaffected by hydrogenation conditions, then the *N*-benzyl group may be removed by hydrogenolysis using a palladium on carbon catalyst in a solvent such as ethanol and in the presence of hydrogen gas or a hydrogen donor such as formic acid. Occasionally it may be preferred that one of the substituents R^3 be a halogen or another substituent defined above which would be reactive under hydrogenation conditions. In these cases, the compound of general formula **32** is reacted with 1-chloroethyl chloroformate in an inert solvent such as toluene at temperatures between room temperature and 110°C (Olafson, R.A. et al. *J. Org. Chem.* 1984, 49, 2081). The toluene is then removed, and the residue is heated in methanol for a period of 15-60 minutes, and the product is the debenzylated

pyrrolidine of general formula 35. The resulting pyrrolidine 35 is then protected as its *tert*-butyl carbamate (36) using BOC anhydride in the presence of a base and a suitable solvent. For example, this can be accomplished in a two phase mixture of chloroform and aqueous sodium bicarbonate as shown in reaction Scheme H.

- 5 The oxazolidinone chiral auxilliary is next hydrolyzed from the pyrrolidines of general formula 36 as shown at the bottom of reaction Scheme H. The hydrolysis reaction is accomplished using lithium hydroperoxide generated *in situ* from lithium hydroxide and 30% aqueous hydrogen peroxide. The reaction is typically conducted in a solvent system such as aqueous THF, and the reaction is
- 10 performed at temperatures between 0°C and room temperature for a period of 1-6 hours. The resulting carboxylic acids of general formula 37 correspond to carboxylic acids of general formula 2 where both *r* and *s* are 1. Using the methodology presented in reaction Scheme A, the compounds of general formula 37 may then be converted to the compounds of the present invention of structural formula I.

Scheme H

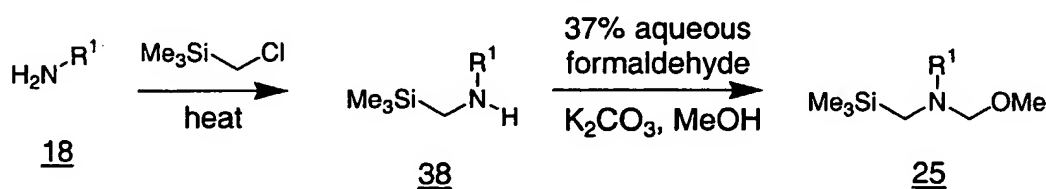


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- As noted previously in the discussion of reaction Scheme D, it may occasionally be preferable to incorporate the R¹ substituent into the substituted pyrrolidine of general formula 37 at an earlier stage of the synthesis, for instance when it is desired that R¹ be a *tert*-butyl group. In such cases, it is possible to utilize
- 20 an azomethine ylid precursor (25) bearing the desired R¹ substituent in the

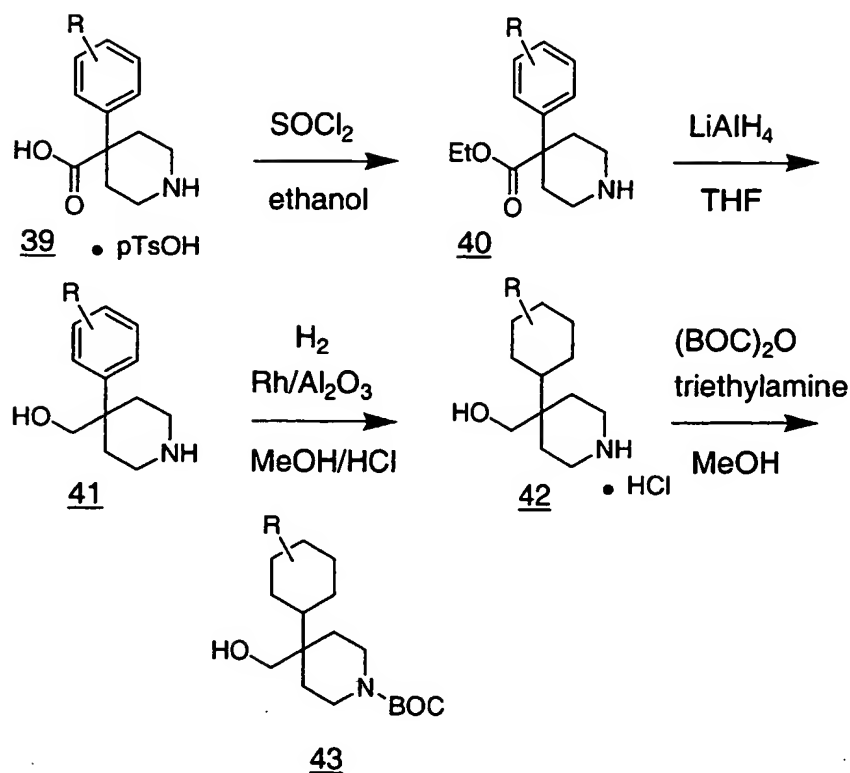
cycloaddition reactions illustrated in reaction Schemes F and G. Reaction Scheme I illustrates the preparation of azomethine precursors of formula 25 starting with amines of general formula 18. Reaction of the amine of formula 18 with chloromethyltrimethylsilane at high temperature and in the absence of solvent affords the *N*-trimethylsilylmethyl-substituted amine of general formula 38. Subsequent reaction of 38 with aqueous formaldehyde in the presence of methanol and a base such as potassium carbonate then affords the generalized ylid precursor 25 which can be utilized in the cycloaddition reactions discussed above.

Scheme I



Reaction Schemes J and K illustrate additional methods for the synthesis of the 4-substituted piperidines of general formula 1 which are required in the amide bond coupling step illustrated in reaction Scheme A. As shown in Reaction Scheme J, treatment of an ethanol solution of carboxylic acid 39, wherein R is hydrogen, C₁-C₆ alkyl or C₁-C₃ polyfluoroalkyl, with a chlorinating agent such as thionyl chloride at a temperature of 65-78° C, preferably 78° C, for a period of 12-24 hours gives the corresponding ethyl ester derivative 40. Ester 40 can be further reacted with a strong reducing agent such lithium aluminum hydride, diisobutylaluminum hydride or equivalent hydride sources in an inert organic solvent such as tetrahydrofuran at 0-25° C for a period of 2-12 hours to provide alcohol 41. Hydrogenation of the aromatic ring in 41 is effected by treatment with hydrogen at a pressure of 1500 pounds per square inch in an inert solvent such as acidic methanol at a temperature of 100°C for a period of 15-24 hours. Suitable catalysts for this hydrogenation reaction include rhodium on alumina and the product is a cyclohexyl substituted derivative of general formula 42. Protection of the amine as the *tert*-butyl carbamate by treatment with di-*tert*-butyl dicarbonate and an amine base such as triethylamine, *N,N*-diisopropylethylamine or the like in an inert organic solvent such as methanol at room temperature for a period of 10-14 hours gives 43.

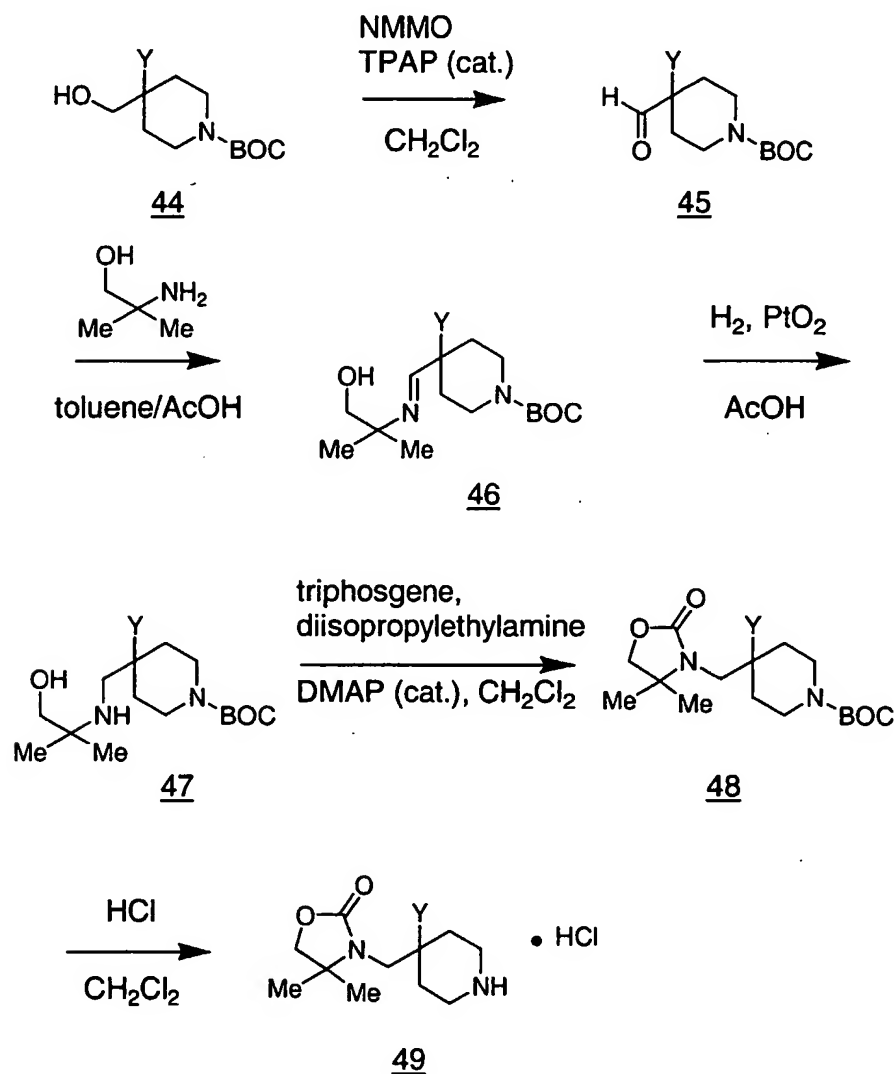
Scheme J



As shown in Reaction Scheme K, alcohols of general formula 44 can be converted to the corresponding aldehydes 45 by treatment with a mild oxidizing agent such as tetrapropylammonium perruthenate (TPAP) in catalytic amounts along with a re-oxidant such as 4-methylmorpholine *N*-oxide (NMMO) in an inert organic solvent such as methylene chloride at a temperature of 0-25° C for a period of 2-6 hours. Aldehydes 45 may be condensed with an amine such as 2-amino-2-methyl-1-propanol by mixing the two agents in a solvent such as toluene, benzene or the like along with an acid catalyst such as acetic acid, p-toluenesulfonic acid or the like at refluxing temperature to allow for azeotropic removal of the water formed in the reaction which furnishes imine 46. Reduction of 46 to the amino alcohol 47 can be effected by treatment with hydrogen and an appropriate catalyst such as platinum oxide on carbon, palladium on carbon, palladium hydroxide on carbon or the like with or without an acid catalyst such as acetic acid in an inert organic solvent such as acetic acid, methanol, and ethanol at room temperature for a period of 8-24 hours. Compound 47 can be converted to the corresponding oxazolidinone 48 by treatment

- with an appropriate acylating agent such as triphosgene along with an amine base such as *N,N*-diisopropylethylamine, triethylamine or the like, and a catalyst such as 4-dimethylaminopyridine in an inert organic solvent such as methylene chloride at a temperature of 0-25° C for a period of 2-4 hours. Finally, deprotection of the
- 5 piperidine nitrogen by treatment with a protic acid such as hydrochloric acid, trifluoroacetic acid or the like in an inert organic solvent such as methylene chloride at or around room temperature for a period of 8-24 hours provides the desired amine 49.

Scheme K

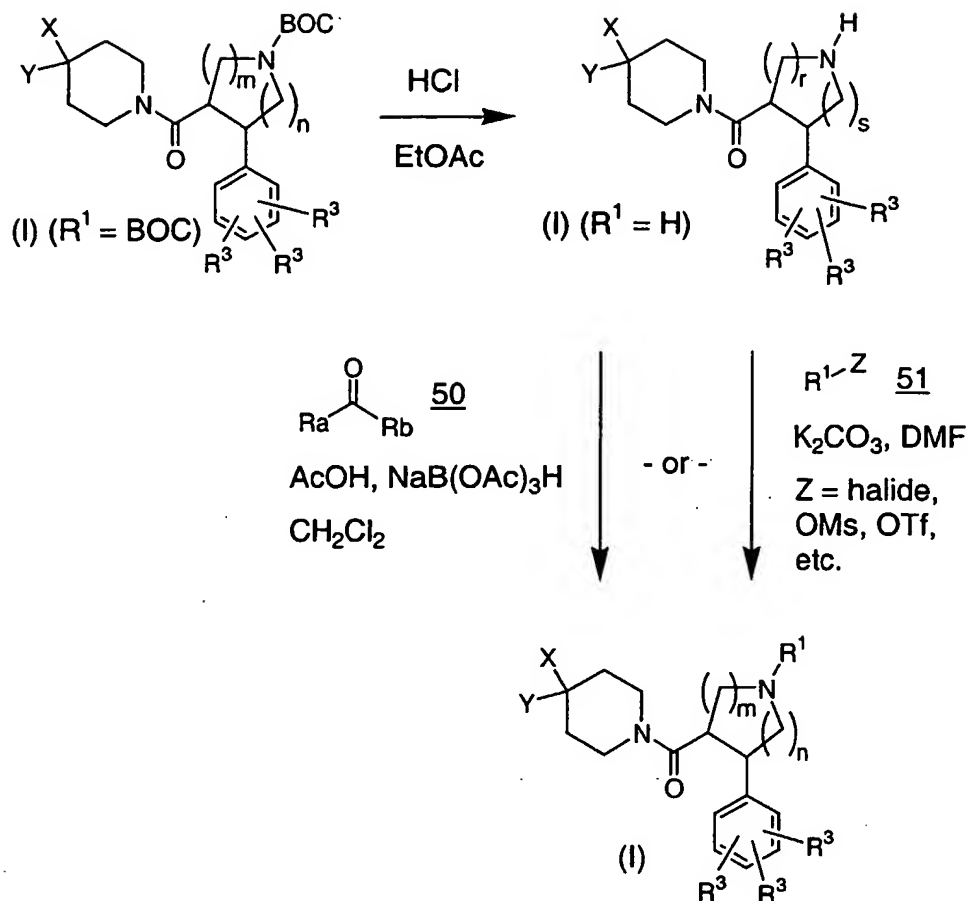


Reaction Scheme L illustrates general methods for the elaboration of an R^1 substituent following assembly of a compound of structural formula I (wherein $R^1 = \text{BOC}$) as described in reaction Scheme A. The *N*-BOC protected compound of structural formula I is first deprotected under acidic conditions for instance by

5 treatment with hydrochloric acid in ethyl acetate or using trifluoroacetic acid in methylene chloride. The resulting heterocyclic compound of structural formula I ($R^1 = \text{H}$) may then be subjected to one of several alkylation strategies known in organic chemistry. For instance, compounds (I) ($R^1 = \text{H}$) may be utilized in a reductive

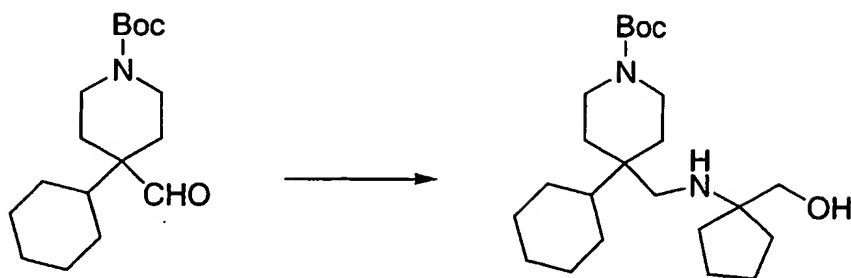
10 amination reaction with a suitable carbonyl containing partner (50). The reductive amination is achieved by initial formation of an imine between the amine of formula I ($R^1 = \text{H}$) and either an aldehyde or ketone of formula 50. The intermediate imine is then treated with a reducing agent capable of reducing carbon-nitrogen double bonds such as sodium cyanoborohydride or sodium triacetoxyborohydride and an alkylated

15 product of structural formula I is produced. Alternatively, a heterocyclic compound of structural formula (I) ($R^1 = \text{H}$) may be directly alkylated using an alkylating agent such as 51 in a polar aprotic solvent such as DMF. In this reaction, the substituent Z of compound 51 is a good leaving group such as a halide, mesylate or triflate and the product is the compound of structural formula I bearing the R^1 substituent.

Scheme LPreparation of 4-Substituted Piperidine Intermediates:

The preparation of other 4-substituted piperidine intermediates of general formula 1 for coupling with the carboxylic acids of general formula 2 as shown in Scheme A below is disclosed in PCT International Application WO 00/74679 (14 December 2000), which is incorporated by reference herein in its entirety. The preparation of additional 4-substituted piperidine intermediates needed to derive the compounds of the present invention is provided below.

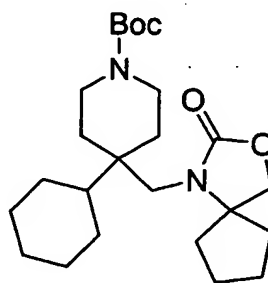
10 PIPERIDINE INTERMEDIATE 1:



To a solution of 4-cyclohexyl 4-formyl-N-(tertbutyloxycarbonyl)-piperidine (2.56 g, 8.68 mmol) in toluene (100 ml) was added acetic acid (2 ml) and 1-amino-1-cyclopentanemethanol (1.0 g, 8.68 mmol). After refluxing by using a Dean-Stark apparatus for 11 hours, the reaction mixture was concentrated. The residue was dissolved in acetic acid (70 ml) and hydrogenated overnight in the presence of platinum oxide (500 mg) under a balloon atmosphere of hydrogen gas. The catalyst was filtered off and solvent was removed to give a colorless oil, which was dissolved in methanol and made basic by addition of NaOH (5N, 4 ml) and concentrated. The residue was partitioned between water and CH₂Cl₂, the two layers separated, and the aqueous layer extracted with CH₂Cl₂. The combined organic extracts were washed with brine, dried over MgSO₄ and concentrated to give the title compound as a colorless oil (2.1 g).

MS: calc. for C₂₃H₄₂N₂O₃: 394.3; Found: 395 (M+1), 417 (M+Na).

PIPERIDINE INTERMEDIATE 2:

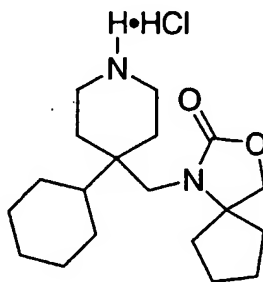


To a solution of Intermediate 1 (2.1 g, 5.33 mmol) in CH₂Cl₂ (70 ml) at 0° was added DMAP (0.65 g, 5.33 mmol), DIEA (3.76 ml, 21.3 mmol) followed by slow addition of phosgene (4.1 ml, 8.0 mmol). After stirring the reaction mixture for one hour at 0°C, the ice-water bath was removed and the reaction mixture was continued to stir at room temperature overnight. The mixture was diluted with

CH_2Cl_2 , washed with water and brine, dried over MgSO_4 and concentrated to give crude product, which was purified by column chromatography on silica gel (2% $\text{EtOAc}/\text{CH}_2\text{Cl}_2$ to 5% $\text{EtOAc}/\text{CH}_2\text{Cl}_2$) to give the title compound as a white solid (1.2 g).

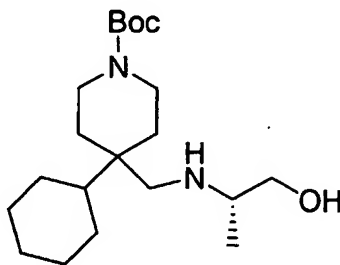
5 MS: calc. for $\text{C}_{24}\text{H}_{40}\text{N}_2\text{O}_4$: 420.3; Found: (M+1), (M+Na).

PIPERIDINE INTERMEDIATE 3:



To the Intermediate 2 (1.2 g) was added hydrogen chloride (4.0 M in dioxane). The reaction mixture was stirred at room temperature for 30 minutes and the solvent was removed *in vacuo* to afford the title compound (1.2 g).
 10 MS: calc. for $\text{C}_{19}\text{H}_{32}\text{N}_2\text{O}_2$: 320.3; Found: 321.1 (M+H).

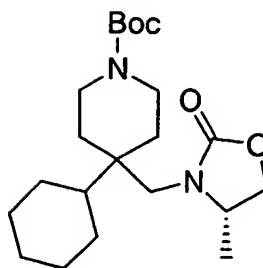
PIPERIDINE INTERMEDIATE 4:



15

Intermediate 4 was prepared from (S)-(+)-2-amino-1-propanol in an analogous manner to the one described for the preparation of Intermediate 1.
 MS: calc. for $\text{C}_{20}\text{H}_{38}\text{N}_2\text{O}_3$: 354; Found: 355 (M+H).

20 PIPERIDINE INTERMEDIATE 5:

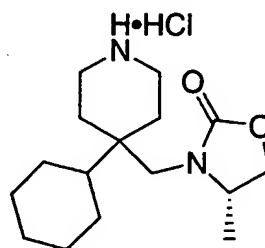


Intermediate 5 was prepared from Intermediate 4 in an analogous manner to the one described for the preparation of Intermediate 2.

MS: calc. for $C_{21}H_{36}N_2O_4$: 380.3; Found: 381 (M+H).

5

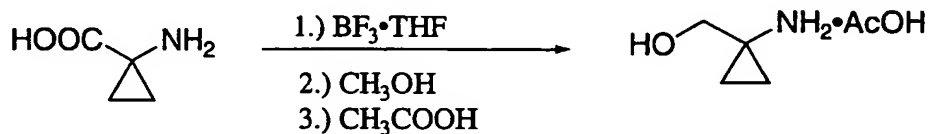
PIPERIDINE INTERMEDIATE 6:



Intermediate 6 was prepared from Intermediate 5 in an analogous manner to the one described for the preparation of Intermediate 3.

10 MS: calc. for $C_{16}H_{28}N_2O_2$: 280.3; Found: 281 (M+H).

PIPERIDINE INTERMEDIATE 7:

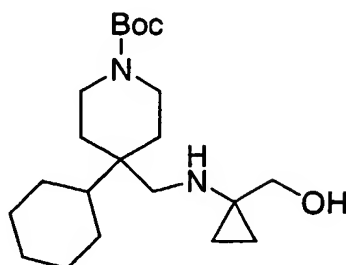


15

To a suspension of 1-aminocyclopropane-1-carboxylic acid (2.8 g, 27.7 mmol) in THF (20 ml) was added borane-tetrahydrofuran complex (100 ml, 100 mmol) slowly under nitrogen at room temperature. The reaction mixture was stirred at 70°C overnight, then cooled to 0°C. After addition of methanol (12.2 ml, 300 mmol), the mixture was allowed to stir for 30 minutes. Then acetic acid (1.6 ml, 27.7

mmol) was added. The reaction mixture was concentrated to provide the title compound as a colorless oil (3.0 g).

PIPERIDINE INTERMEDIATE 8:

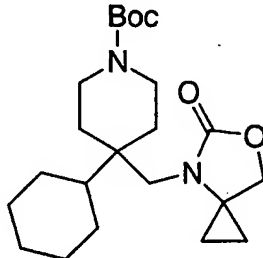


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Intermediate 8 was prepared from Intermediate 7 in an analogous manner to the one described for the preparation of Intermediate 1.

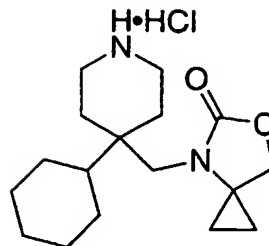
MS: calc. for $C_{21}H_{38}N_2O_3$: 366.3; Found: 367 (M+H).

10 PIPERIDINE INTERMEDIATE 9:



- 15 To a solution of Intermediate 8 (0.8 g, 2.18 mmol) in CH_2Cl_2 (40 ml) at 0° was added DMAP (0.266 g, 2.18 mmol), DIEA (1.52 ml, 8.74 mmol) and triphosgene (0.648 g, 2.18 mmol). After stirring the reaction mixture for one hour at $0^\circ C$, the ice-water bath was removed and the reaction mixture was allowed to stir at r.t. overnight. The mixture was diluted with CH_2Cl_2 , washed with water and brine, dried over $MgSO_4$ and concentrated to give crude product, which was purified by column chromatography on silica gel (10% $CH_2Cl_2/EtOAc$) to give the title compound as a colorless oil (0.13 g).
- 20 ESI-MS: calc. for $C_{22}H_{36}N_2O_4$: 392; Found: 393 (M+1).

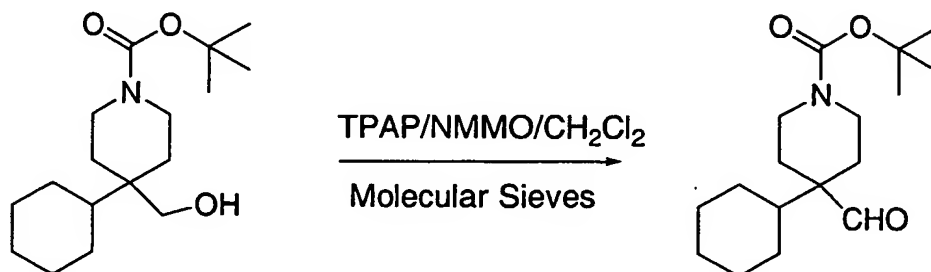
PIPERIDINE INTERMEDIATE 10:



Intermediate 10 was prepared from Intermediate 9 in an analogous manner to the one described for the preparation of Intermediate 3.
MS: calc. for $C_{17}H_{28}N_2O_2$: 292.2; Found: 293 (M+H).

5

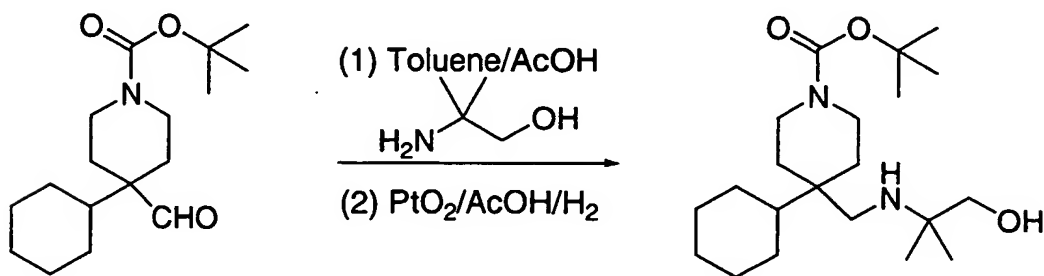
PIPERIDINE INTERMEDIATE 11:



To a solution of the alcohol (9.41 g, 31.6 mmol) in CH_2Cl_2 (100 ml) at $0^\circ C$ containing molecular sieves (2 g) and 4-methylmorpholine N-oxide (NMMO) (4.449 g, 37.98 mmol) was added TPAP (1.12 g, 3.16 mmol). After stirring the reaction mixture at $0^\circ C$ for 0.5h, the reaction mixture was warmed to room temperature and stirred further for 5 hrs. The reaction mixture was concentrated to half the volume, diluted with hexane (250 ml), filtered through a silica gel pad and concentrated to give pure title compound (9.4 g).

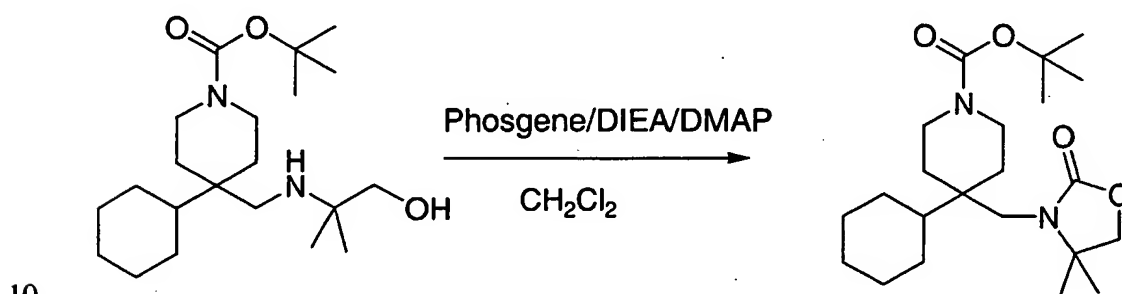
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PIPERIDINE INTERMEDIATE 12:



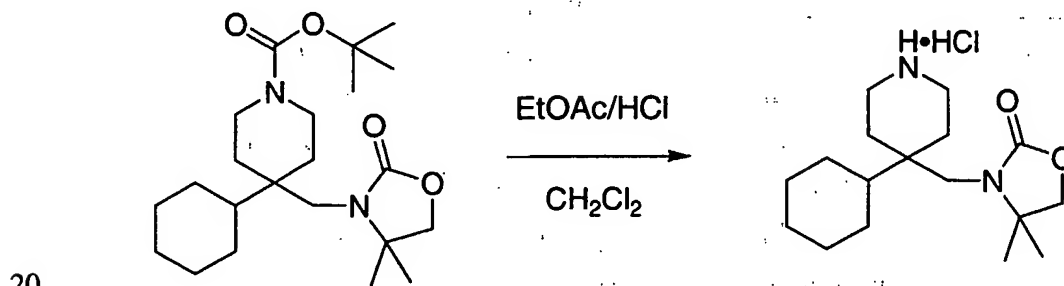
To a solution of the aldehyde (2 g, 6.7 mmol) in toluene (50 ml) was added acetic acid (500 μ l). After stirring the reaction mixture at reflux temperature using Dean Stark apparatus for 8 hrs, the mixture was concentrated and dissolved in acetic acid (30 ml). To the mixture was added PtO_2 (500 mg) which was stirred under an atmosphere of H_2 overnight. The reaction mixture was flushed with nitrogen, filtered and concentrated to give the title compound (2 g).

PIPERIDINE INTERMEDIATE 13:



To a solution of the amino alcohol (4.96 g, 13.47 mmol) in CH_2Cl_2 at 0°C containing DIEA (6.98 g, 53.9 mmol), DMAP (1.64 g, 13.47 mmol) was added slowly a toluene solution of phosgene (1.93M, 10.47 ml, 20.21 mmol). After stirring the reaction mixture for 1 hr at 0°C , the temperature was raised to room temperature and stirred further for 2 hrs. The reaction mixture was diluted with CH_2Cl_2 , washed with water, brine, dried and concentrated. The residue was purified by column chromatography over silica gel (5% EtOAc/ CH_2Cl_2) to give pure product (3.95 g).

PIPERIDINE INTERMEDIATE 14:

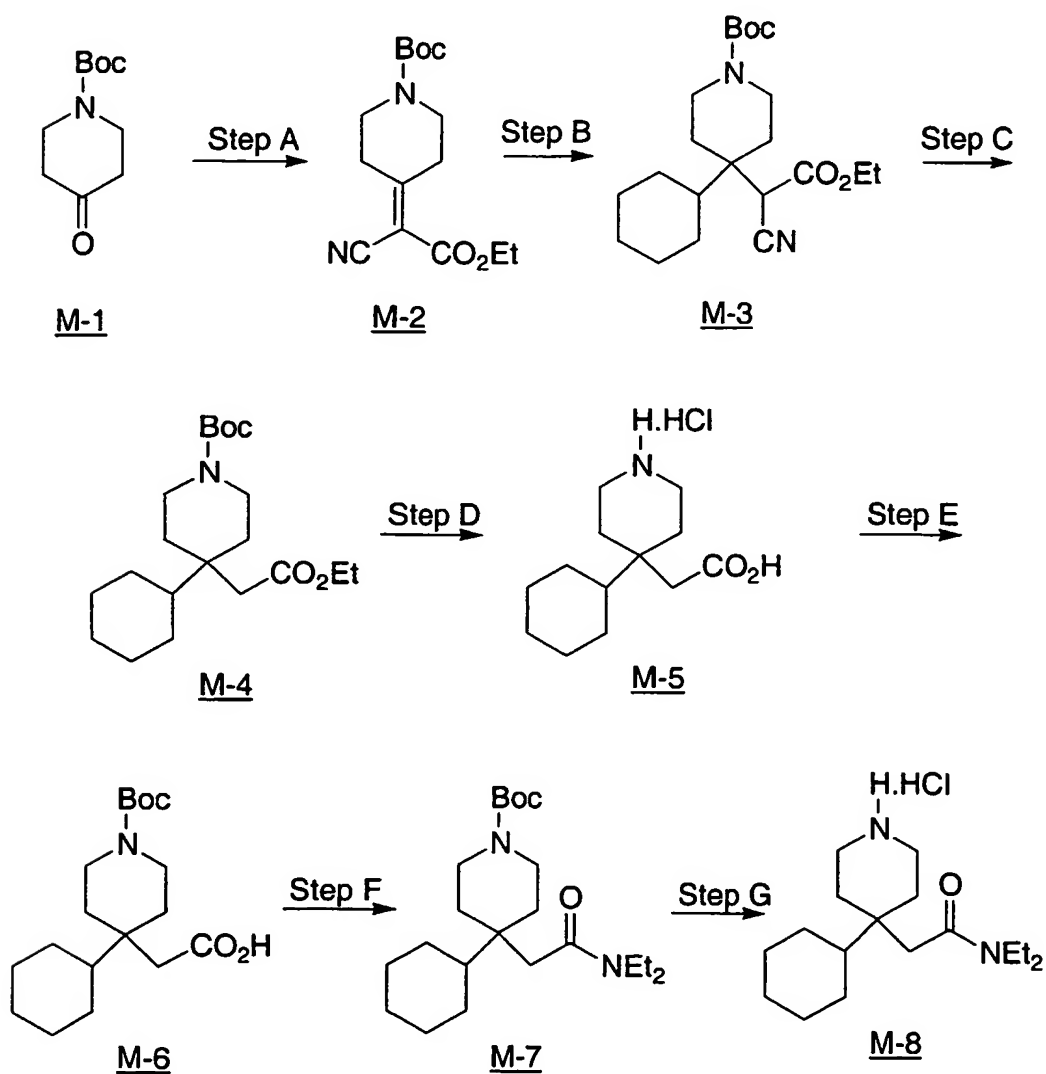


To a solution of Intermediate 13 (3.95 g) in CH_2Cl_2 was added 5 ml of a saturated HCl solution in EtOAc. After stirring the reaction mixture for 30 min at room temperature, the solvent was removed and the residue lyophilized from a benzene/methanol solution to afford the title compound (3.85 g).

5

PIPERIDINE INTERMEDIATE 15:

Scheme M



10

Step A:

- To a 500-mL round-bottom flask equipped with a Dean Stark trap and magnetic stirrer was added 1-Boc-4-piperidone (M-1) (20.0 g, 100 mmol), cyanoacetic acid ethyl ester (10.6 mL, 100 mmol), NH₄OAc (0.77 g, 10 mmol), HOAc (0.57 mL, 10 mmol), and benzene (200 mL). The mixture was stirred at reflux temperature overnight. After cooling to room temperature, the volatiles were removed under reduced pressure, and the residue was purified by flash column chromatography with 20% EtOAc in hexane as eluent to give M-2 as white solid (21.6 g).
- ESI-MS: Calcd. for C₁₅H₂₂N₂O₄: 294; Found: 317 (M⁺+Na).

Step B:

- To a suspension of CuCN (3.28 g, 36.3 mmol) in dry THF (100 mL) was added cyclohexylmagnesium chloride (36.6 mL, 73.2 mmol, 2.0 N in ether). The resulting suspension was stirred at -50 °C for 30 min and then warmed up to room temperature. After stirring for 1 h, a solution of compound M-1 (5.40 g, 18.3 mmol) in 50 mL of THF was cannulated into the mixture over 2 min. The mixture was stirred at -50 °C for 1 h and then kept at -25 °C overnight. The mixture was slowly warmed to -10 °C and quenched with saturated aqueous NH₄Cl (50 mL) and water (50 mL), extracted with EtOAc (2 x 250 mL). The combined organic extracts were washed three times with water, 1 N HCl, saturated aqueous NaHCO₃, dried over MgSO₄, filtered, and evaporated to give compound M-3 as a colorless oil (7.12 g).
- ESI-MS: Calcd. for C₂₁H₃₄N₂O₄: 378; Found: 401 (M⁺+Na).

Step C:

- A mixture of M-3 (6.91 g, 18.3 mmol), LiCl (1.09 g, 25.6 mmol), water (1.40 mL), and DMSO (100 mL) was stirred at 160 °C for 1 h. After cooling to room temperature, the mixture was poured into water (800 mL) and extracted with Et₂O (4 x 250 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography with 20% EtOAc in hexane as eluent to give compound M-4 as a colorless oil (2.83 g).
- ESI-MS: Calcd. for C₁₈H₃₀N₂O₂: 306; Found: 329 (M⁺ + Na).

Step D:

To a solution of 4.0 N HCl in dioxane (30 mL, 120 mmol) was added M-4 (2.60 g, 8.48 mmol). The mixture was stirred at room temperature for 1 h and the volatiles were removed under reduced pressure. The residue was dissolved in a concentrated HCl (100 mL). The mixture was stirred overnight at reflux temperature.

- 5 After cooling to room temperature, the volatiles were removed under reduced pressure to give the compound M-5 as a yellow solid (2.42 g).

ESI-MS: Calcd. for $C_{13}H_{23}NO_2$: 225; Found: 226 ($M^+ + 1$)

Step E:

- 10 To a solution of compound M-5 (1.91 g, 8.48 mmol) in dioxane (50 mL) and water (50 mL, containing 5.0 mL 5.0 N NaOH, 25 mmol) was added di-tert-butyl dicarbonate (2.22 g, 10.2 mmol). The mixture was stirred at room temperature for 4 h and the volatiles were removed under reduced pressure. The residue was quenched with a mixture of EtOAc (200 mL) and 1 N HCl (50 mL). The layers were
15 separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and evaporated to give M-6 as a white solid (2.97 g).

ESI-MS: Calcd. for $C_{18}H_{31}NO_4$: 325; Found: 326 ($M^+ + 1$)

20 Step F:

- Compound M-6 (1.0 g, 3.07 mmol) was dissolved in 30 mL of methylene chloride, and then diethylamine (0.38 mL, 3.68 mmol), DMAP (0.037 g, 0.307 mmol), EDC (1.18 g, 6.14 mmol) were added. The resulting mixture was stirred at room temperature overnight, and then diluted with 20 mL of CH_2Cl_2 and
25 washed with 20 mL of 1N HCl solution, 20 mL of saturated $NaHCO_3$ solution, 20 mL of H_2O , and 20 mL of saturated NaCl solution. The organic phase was dried over $MgSO_4$, filtered, and evaporated to give M-7 (1.16 g).

ESI-MS: Calcd. for $C_{22}H_{40}N_2O_3$: 380; Found: 381 ($M^+ + 1$)

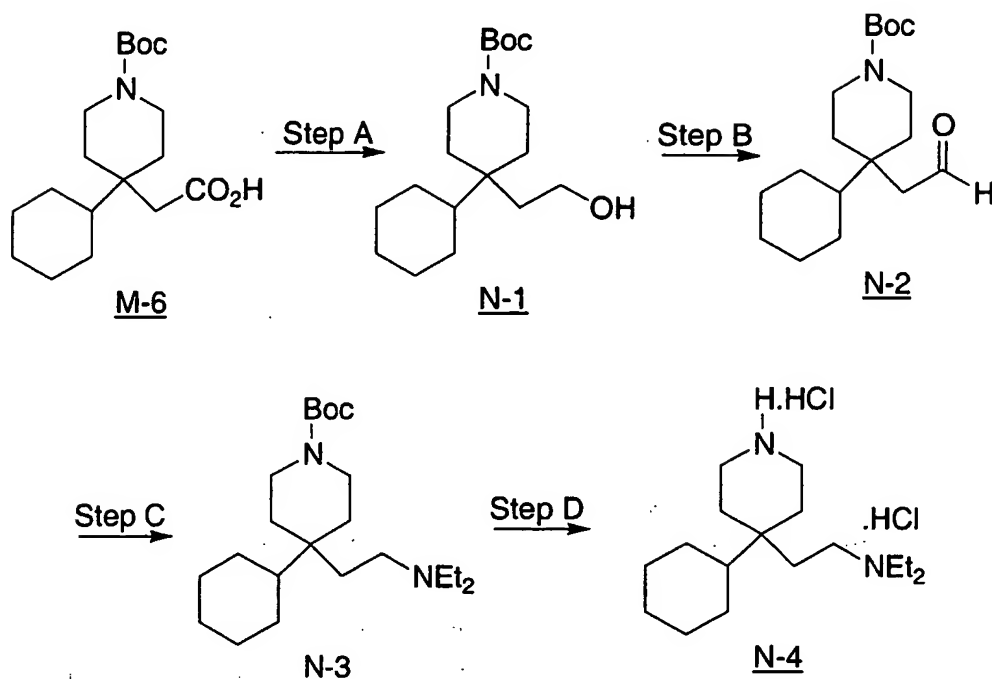
30 Step G:

- To a solution of 4.0 N HCl in dioxane (30 mL, 120 mmol) was added M-7 (1.16 g, 3.07 mmol). The mixture was stirred at room temperature for 1 h and the volatiles were removed under reduced pressure to give M-8 (0.99 g).

ESI-MS: Calcd. for $C_{17}H_{32}N_2O$: 280; Found: 281 ($M^+ + 1$)

35

PIPERIDINE INTERMEDIATE 16:

Scheme NStep A:

- 5 To a solution of M-6 (0.18 g, 0.554 mmol) in 8.0 mL of dry THF was added borane-dimethyl sulfide complex (1.10 mL, 2.0 N in THF, 2.20 mmol). The mixture was stirred overnight and then quenched with MeOH. The volatiles were removed under reduced pressure to give N-1 (0.11 g).

ESI-MS: Calcd. for $C_{18}H_{33}NO_3$: 311; Found: 334 ($M^+ + Na$).

10

Step B:

- To a suspension of N-1 (0.11 g, 0.347 mmol), 4-methylmorpholine N-oxide (0.049 mg, 0.416 mmol), and molecular sieve in dry methylene chloride (5.0 mL) was added tetrapropylammonium perruthenate (0.012 g, 0.035 mmol). After stirring for 30 min, the mixture was filtered through a pad of silica gel and washed with ether. The organic solution was evaporated to give compound N-2 as an oil (0.11 g).

ESI-MS: Calcd. for $C_{18}H_{31}NO_3$: 309; Found: 332 ($M^+ + Na$).

Step C:

To a solution of N-2 (0.11 g, 0.35 mmol) in 3.0 mL of methylene chloride was added diethylamine (0.072 mL, 0.70 mmol) and molecular sieves. After stirring for about 5 min, Na(OAc)₃BH (0.22 mg, 1.05 mmol) was added and the mixture was stirred for 6 h at room temperature. After filtration of molecular sieves, the mixture was diluted with methylene chloride, washed twice with saturated aqueous NaHCO₃ solution, dried over anhydrous Na₂SO₄, filtered, and evaporated to give N-3 (0.080 g).

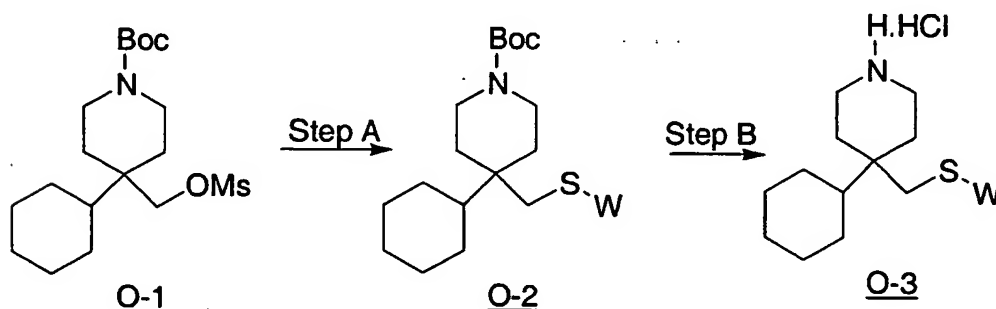
ESI-MS: Calcd. for C₂₂H₄₂N₂O₂: 366; Found: 367 (M⁺ + 1).

Step D:

To a solution of 4.0 N HCl in dioxane (10 mL, 40 mmol) was added compound N-3 (0.080 g, 0.218 mmol). The mixture was stirred at room temperature for 1 h and the volatiles were removed under reduced pressure to give N-4 (0.075 g).

ESI-MS: Calcd. for C₁₇H₃₄N₂: 266; Found: 227 (M⁺ + 1)

PIPERIDINE INTERMEDIATES 17-21:

Scheme O

W = iPr, Me, Et, n-Pr,
cyclopropylmethyl, or cyclobutyl

Step A:

To a stirred solution of tert-butyl 4-cyclohexyl-4-[[[(methylsulfonyl)oxy]methyl]piperidine-1-carboxylate (O-1) (3 g, 8.0 mmol) in DMF (30 mL) at room temperature was added sodium 2-methyl-2-propanethiolate (0.78 g, 8.0 mmol). The resultant suspension was stirred at 60°C for 18 h and then poured into water (150 mL) and extracted with diethyl ether (3 x 100mL). The

combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. Flash chromatography over silica (5% EtOAc in hexane) yielded O-2 (W = iPr) as a clear colorless oil (2.4 g).

Mass Spectrum (ESI): calcd for $\text{C}_{20}\text{H}_{37}\text{NO}_2\text{S}$: 355.25; Found: 378 ($\text{M}^+ + \text{Na}$).

5

Step B:

To a stirred solution of O-2 (W = iPr) (2.4 g, 6.7 mmol) in methylene chloride (10 mL) at room temperature was added HCl (5N in dioxane) (50 mL). The resultant solution was stirred at room temperature for 1 h. Volatiles were removed *in vacuo* to furnish O-3 (W = iPr) as a clear colorless gum (1.9 g).

10

Mass Spectrum (ESI): calcd for $\text{C}_{15}\text{H}_{29}\text{NS}$: 255.20; Found: 256 ($\text{M}^+ + 1$).

The piperidine intermediates O-3 (W = Me, Et, n-Pr, cyclopropylmethyl, and cyclobutyl) were prepared in an analogous manner to the one described for the preparation of 4-cyclohexyl-4-[(isopropylthio)methyl]piperidinium chloride (O-3, W = iPr).

15

O-3 (W = Et): Mass Spectrum (ESI): calcd for $\text{C}_{14}\text{H}_{27}\text{NS}$: 241.19; Found: 242 ($\text{M}^+ + 1$).

O-3 (W = Me): Mass Spectrum (ESI): calcd for $\text{C}_{13}\text{H}_{25}\text{NS}$: 227.17; Found: 228 ($\text{M}^+ + 1$).

20

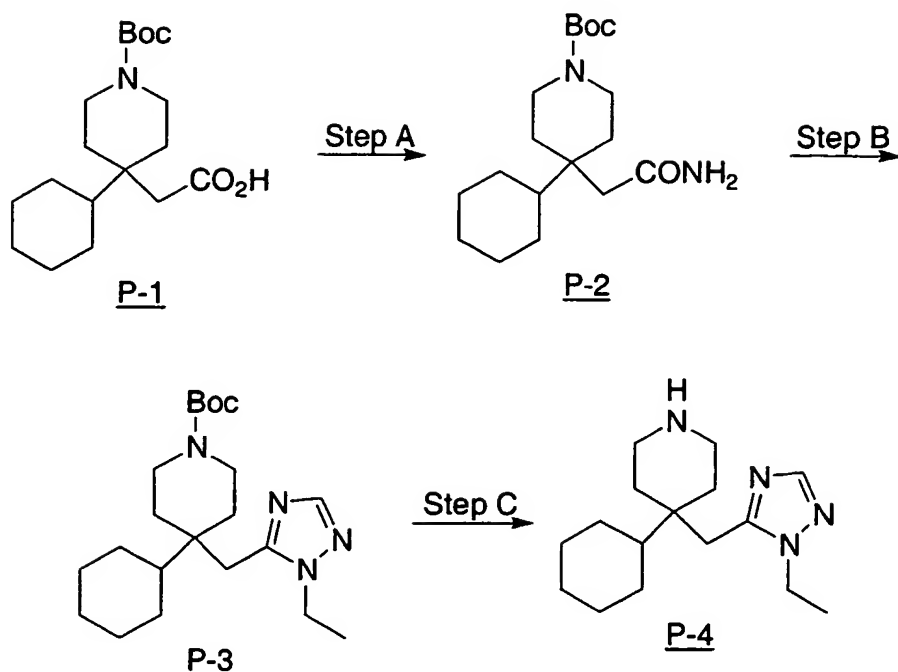
O-3 (W = n-Pr): Mass Spectrum (ESI): calcd for $\text{C}_{15}\text{H}_{29}\text{NS}$: 255.20; Found: 256 ($\text{M}^+ + 1$).

O-3 (W = cyclopropylmethyl): Mass Spectrum (ESI): calcd for $\text{C}_{16}\text{H}_{29}\text{NS}$: 267.20; Found: 268 ($\text{M}^+ + 1$).

O-3 (W = cyclobutylthio): Mass Spectrum (ESI): calcd for $\text{C}_{16}\text{H}_{29}\text{NS}$: 267.20; Found: 268 ($\text{M}^+ + 1$).

25

PIPERIDINE INTERMEDIATE 22:

Scheme PStep A:

To a solution of P-1 (0.745 g, 2.072 mmol) in methylene chloride (40 mL) at 0°C was added DMF (1 mL) followed by the dropwise addition of oxalyl chloride (1.14 mL of 2M solution in methylene chloride, 2.28 mmol). The reaction was warmed to room temperature over one h, then re-cooled to 0°C before transferring to a rapidly stirring saturated aqueous ammonium hydroxide solution (15 mL). The resulting mixture was then poured into methylene chloride (40 mL) and diluted with 1N NaOH (40 mL). The layers were separated and the aqueous phase was extracted three times with methylene chloride. The combined organics were then washed with water and brine, dried (sodium sulfate) and the volatiles removed *in vacuo*. Flash chromatography over silica (25% acetone/methylene chloride) yielded P-2 as a white foam (0.615 g).

Mass Spectrum (ESI): calcd for $C_{21}H_{30}N_2O_3$: 358.23; Found 359 ($M^+ + 1$).

Step B:

A solution of P-2 (0.150 g, 0.84 mmol) in N,N-dimethylformamide dimethyl acetal (1 mL) was refluxed at 120°C for 2 h, then cooled to room

temperature. The reaction was then concentrated and the residue was dissolved in acetic acid (1 mL). Ethyl hydrazine was then added and the reaction was heated at 95°C for 3.5 h. The volatiles were then removed *in vacuo* and the reaction was partitioned between sodium bicarbonate and ethyl acetate. The organics were collected, washed with water and brine, dried (sodium sulfate), and the volatiles removed *in vacuo*. Purification by flash chromatography (0-15% acetone in methylene chloride) yielded P-3 as a pale yellow oil (79 mg).

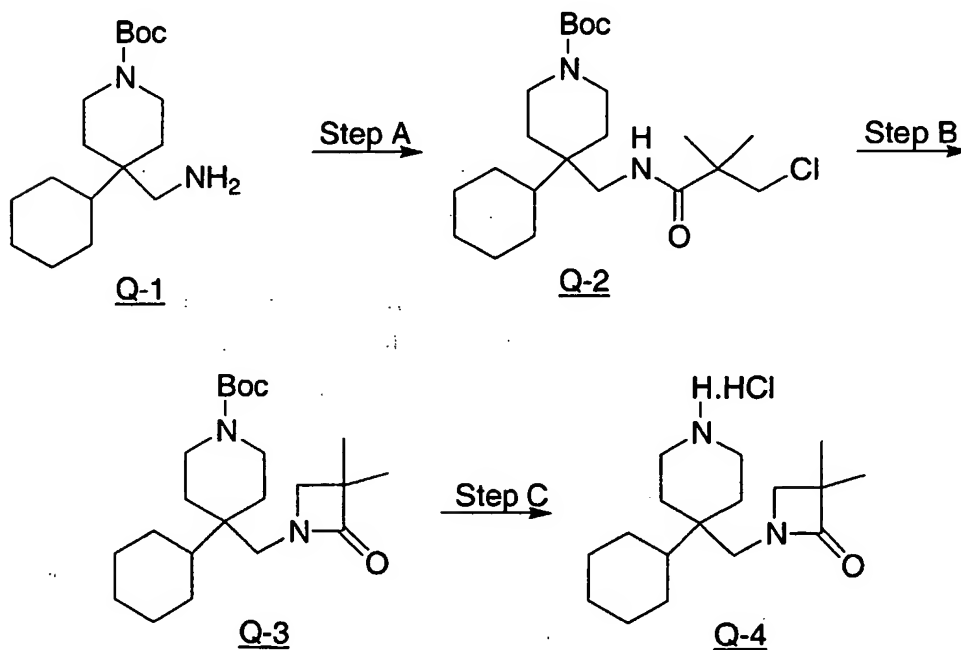
Mass Spectrum (ESI): calcd for $C_{24}H_{34}N_4O_2$: 410.27; Found 411 ($M^+ + 1$).

10 Step C:

To a solution of P-3 (79 mg) in methylene chloride was added 30% HBr in acetic acid (5 mL) and the reaction was stirred for two hours. The volatiles were removed, and the reaction was partitioned between 1N NaOH and methylene chloride. The organics were dried (sodium sulfate) and evaporated to afford P-4 as an oil (59 mg). Mass Spectrum (ESI): calcd for $C_{16}H_{28}N_4$: 276.23; Found 277 ($M^+ + 1$).

PIPERIDINE INTERMEDIATE 23:

Scheme Q



Step A:

To a stirred solution of Q-1 (1.33 g, 4.5 mmol) in methylene chloride (12 mL) was added DMAP (0.14 g, 1.1 mmol) and 3-chloropivaloyl chloride (0.87 g, 5.6 mmol). The mixture was stirred 1 h, diluted with methylene chloride, washed with 1N HCl, the organic layer dried over MgSO₄ and the solvent removed *in vacuo* to provide 2.1 g of Q-2 as an oil. ESI-MS calc. for C₂₂H₃₉ClN₂O₃: 414; Found 415 (M+H).

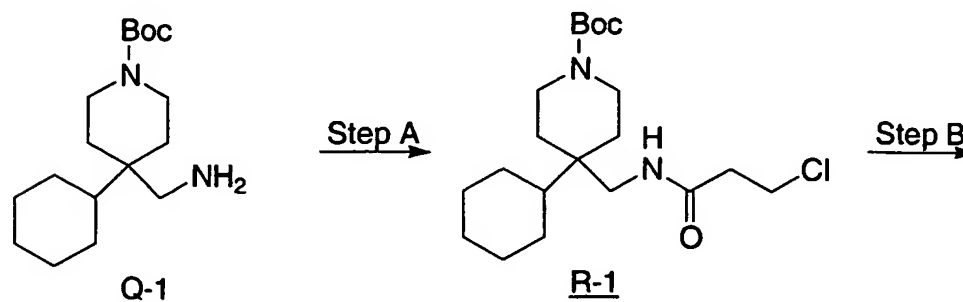
Step B:

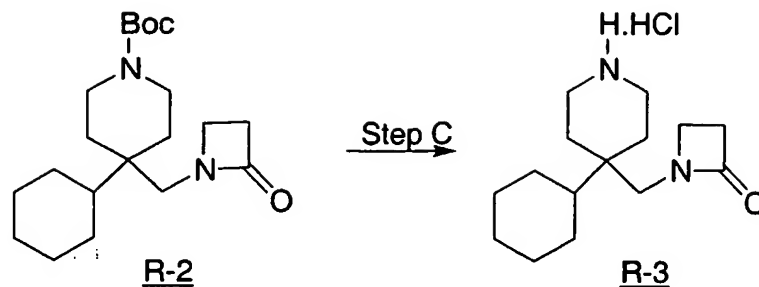
To a stirred solution of Q-1 (2.25 g, 5.42 mmol) in DMF (15 mL) was added NaH (0.52 g, 21.7 mmol) and heated to 70°C for 16 h. The mixture was quenched with MeOH and then water. The mixture was concentrated, diluted with EtOAc, washed with 2N HCl, brine, dried over MgSO₄ and evaporated. The product was purified by preparative HPLC (C18, 20 x 100mm, 50-100% acetonitrile) to provide 850 mg of Q-3 as a yellow solid. ESI-MS calc. for C₂₂H₃₈N₂O₃: 378; Found 379 (M+H).

Step C:

Compound Q-3 (1.05 g, 1.92 mmol) was treated with HCl-EtOAc solution at room temperature for 30 min. The mixture was evaporated to provide 690 of Q-4 as a solid. ESI-MS calc. for C₁₇H₃₀N₂O: 278; Found 279 (M+H).

PIPERIDINE INTERMEDIATE 24:

Scheme R

Step A:

Compound R-1 was synthesized in a manner similar as Q-2, but using 3-chloropropionyl chloride. ESI-MS calc. for $C_{20}H_{35}ClN_2O_3$: 386; Found 387 (M+H).

5

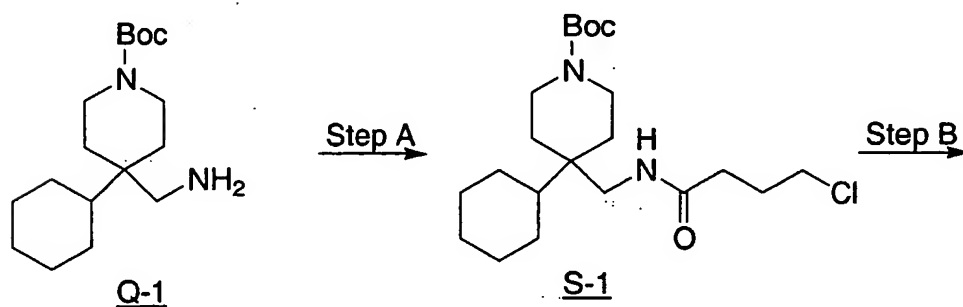
Step B:

Compound R-2 was synthesized from R-1 in a manner similar as Q-3. ESI-MS calc. for $C_{20}H_{34}N_2O_3$: 350; Found 351 (M+H).

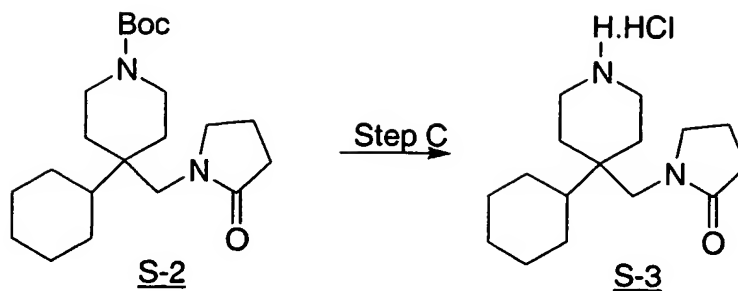
10 Step C:

Compound R-3 was synthesized from R-2 in a manner similar as Q-4. ESI-MS calc. for $C_{15}H_{26}N_2O$: 250; Found 251 (M+H).

PIPERIDINE INTERMEDIATE 25:

Scheme S

15

Step A:

Compound S-1 was synthesized in a manner similar as Q-2, but using 4-chlorobutyl chloride. ESI-MS calc. for $C_{21}H_{37}ClN_2O_3$: 400; Found 401 (M+H).

5

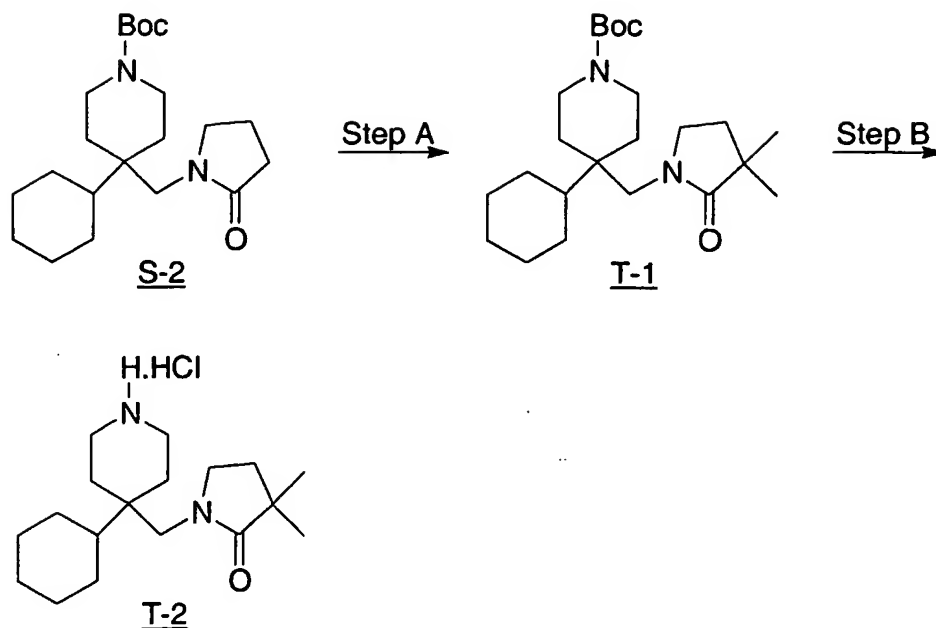
Step B:

Compound S-2 was synthesized from S-2 in a manner similar to Q-3. ESI-MS calc. for $C_{21}H_{36}N_2O_3$: 364; Found 365 (M+H).

10 Step C:

Compound S-3 was synthesized from S-2 in a manner similar to Q-4. ESI-MS calc. for $C_{16}H_{28}N_2O$: 264; Found 265 (M+H).

PIPERIDINE INTERMEDIATE 26:

Scheme TStep A:

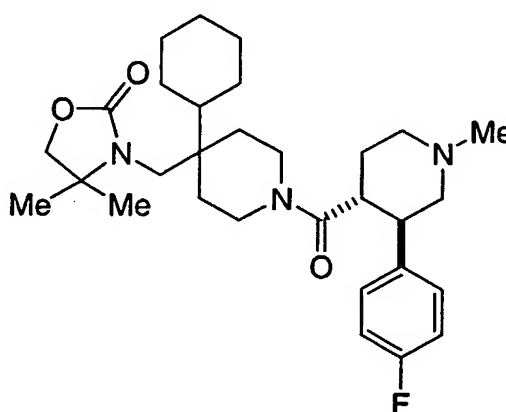
To a stirred solution of S-2 (2.3 g, 6.3 mmol) in THF (20 mL) cooled to -78°C was added lithium diisopropylamide (LDA) (2M solution in THF) (3 eq) slowly via syringe over 20 min and stirring was continued for 1 h. Iodomethane was added and the mixture was stirred for 1 h. The reaction mixture was warmed to room temperature and stirring was continued an additional 30 min. Subsequently, the reaction mixture was cooled again to -45°C and another 1.5 eq. of LDA added, the mixture was stirred 15 min, then an additional 1 eq. of iodomethane was introduced to the reaction mixture and the stirring continued 1 h. The reaction was quenched with water, concentrated and partitioned between EtOAc/2N HCl, washed with brine, dried over MgSO_4 , filtered and concentrated. The residue was chromatographed (silica, 1:4 EtOAc/hexane) to provide 720 mg of T-1 as a white solid. ESI-MS calc. for $\text{C}_{23}\text{H}_{40}\text{N}_2\text{O}_3$: 392; Found 393 (M+H).

Step B:

Compound T-2 was prepared from T-1 in a manner similar to Q-4. ESI-MS calc. for $\text{C}_{18}\text{H}_{32}\text{N}_2\text{O}$: 292; Found 293 (M+H).

The following Examples are provided to illustrate the invention and are not to be construed as limiting the scope of the invention in any manner.

EXAMPLE 1



(±)-trans-4-((4-cyclohexyl-4-((4,4-dimethyl-2-oxo-1,3-oxazolidin-3-yl)methyl)piperidin-1-yl)carbonyl)-3-(4-fluorophenyl)-1-methylpiperidinium trifluoroacetate

- 10 **Step A:** Preparation of *tert*-butyl (±)-trans-4-((4-cyclohexyl-4-((4,4-dimethyl-2-oxo-1,3-oxazolidin-3-yl)methyl)piperidin-1-yl)carbonyl)-3-(4-fluorophenyl)piperidine-1-carboxylate

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (47.7 mg, 0.249 mmol) was added to a stirred mixture of 4-cyclohexyl-4-((4,4-dimethyl-2-oxo-1,3-oxazolidin-3-yl)methyl)piperidinium chloride (54.9 mg, 0.166 mmol), (±)-trans-1-(*tert*-butoxycarbonyl)-3-(4-fluorophenyl)-piperidine-4-carboxylic acid (70.7 mg, 0.216 mmol), 1-hydroxy-benzotriazole (33.6 mg, 0.249 mmol) and *N*-methylmorpholine (54.8 μ L, 0.498 mmol) in methylene chloride (2.1 mL) at ambient temperature. After approximately 18 h, the reaction mixture was poured into saturated aqueous sodium bicarbonate and extracted three times with methylene chloride. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was used without further purification in the subsequent reaction.

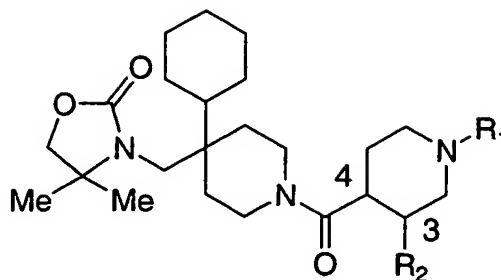
Step B: Preparation of (±)-trans-4-({4-cyclohexyl-4-[(4,4-dimethyl-2-oxo-1,3-oxazolidin-3-yl)methyl]piperidin-1-yl}carbonyl)-3-(4-fluorophenyl)piperidinium trifluoroacetate

5 A saturated solution of hydrogen chloride in ethyl acetate (2.0 mL) was added to a solution of crude product from step A in methylene chloride (1.0 mL) at room temperature. After 18 h, the volatiles were evaporated *in vacuo*, and the crude residue purified by preparative reversed phase high pressure liquid chromatography on a YMC Pack Pro C18 column (gradient elution: 0-100% acetonitrile/water as eluent, 0.1% TFA as modifier) to give the title compound as an off-white solid [MS: *m/z* 500 (MH⁺)].

Step C: Preparation of (±)-trans-4-({4-cyclohexyl-4-[(4,4-dimethyl-2-oxo-1,3-oxazolidin-3-yl)methyl]piperidin-1-yl}carbonyl)-3-(4-fluorophenyl)-1-methylpiperidinium trifluoroacetate

15 Sodium cyanoborohydride (12.6 mg, 0.200 mmol) was added to a vigorously stirred suspension of the product of step B (20.0 mg, 0.040 mmol), paraformaldehyde (20.0 mg), 4 Å sieves (20.0 mg) and acetic acid (45.8 µL, 0.800 mmol) in tetrahydrofuran/methanol (1:3, 400 µL) at ambient temperature. After 18 h, the reaction mixture was poured into saturated aqueous sodium bicarbonate and
20 extracted three times with methylene chloride. The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated *in vacuo*. Purification of the crude residue by preparative reversed phase high pressure liquid chromatography on YMC Pack Pro C18 column (gradient elution; 0-100% acetonitrile/water as eluent, 0.1% TFA as modifier) provided the title compound (12 mg) as an off-white solid
25 (12.0 mg); MS: *m/z* 514 (MH⁺).

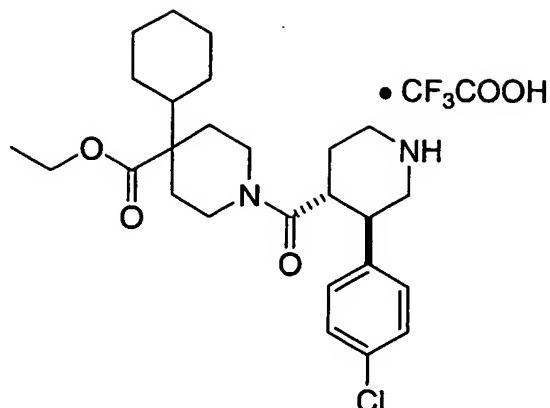
Following a procedure similar to that described above for Example 1, the following compounds can be prepared:



Ex. #	Relative stereo. (3,4)	R1	R2	Parent Ion <i>m/z</i>
2	trans (RS,RS)	-H	4-fluorophenyl	500
3	trans (S,S)	-H	4-fluorophenyl	500
4	trans (R,R)	-H	4-fluorophenyl	500
5	trans (RS,RS)	-CH ₂ C(O)Ot-Bu	4-fluorophenyl	614
6	trans (RS,RS)	-CH ₂ C(O)OH	4-fluorophenyl	558
7	trans (R,R)	isopropyl	4-fluorophenyl	542
8	trans (R,R)	methyl	4-fluorophenyl	514
9	trans (R,R)	n-propyl	4-fluorophenyl	542
10	trans (R,R)	ethyl	4-fluorophenyl	528
11	trans (R,R)	CH(CH ₃)CH ₂ OMe	4-fluorophenyl	572
12	trans (RS,RS)	-H	4-chlorophenyl	516
13	trans (RS,RS)	-H	4-methoxyphenyl	512
14	trans (S,S)	methyl	4-chlorophenyl	530
15	trans (R,R)	methyl	4-chlorophenyl	530
16	trans (RS,RS)	-H	4-methylphenyl	496
17	trans (RS,RS)	-H	4-(4'-chloro-phenyl)phenyl	592
18	trans (RS,RS)	isopropyl	4-chlorophenyl	558
19	trans (R,R)	isopropyl	4-chlorophenyl	559
20	trans (S,S)	isopropyl	4-chlorophenyl	559
21	trans (RS,RS)	cyclobutyl	4-chlorophenyl	570
22	trans (RS,RS)	n-propyl	4-chlorophenyl	558
23	trans (RS,RS)	ethyl	4-chlorophenyl	544
24	trans (R,R)	-C(=NH)NH ₂	4-fluorophenyl	543
25	trans (R,R)	-C(=NH)NH ₂	4-chlorophenyl	559
26	trans (R,R)	-CH ₂ CH ₂ NH ₂	4-chlorophenyl	560

27	trans (R,R)	-CH ₂ CH ₂ NH ₂	4-fluorophenyl	544
28	trans (RS,RS)	-H	4-chloro-3-fluorophenyl	534
29	trans (RS,RS)	isopropyl	4-chloro-3-fluorophenyl	576
30	trans (R,R)	-C(=NH)CH ₃	4-fluorophenyl	541
31	trans (RS,RS)	-H	3-chloro-4-fluorophenyl	535
32	trans (RS,RS)	isopropyl	3-chloro-4-fluorophenyl	577
33	trans (RS,RS)	ethyl	3-chloro-4-fluorophenyl	
34	trans (RS,RS)	-H	2,4-dichlorophenyl	551
35	trans (RS,RS)	isopropyl	2,4-dichlorophenyl	593
36	trans (RS,RS)	-H	3,4-dichlorophenyl	551
37	trans (RS,RS)	isopropyl	3,4-dichlorophenyl	593
38	trans (RS,RS)	-H	2,4-difluorophenyl	519
39	trans (RS,RS)	isopropyl	2,4-difluorophenyl	561
40	trans (RS,RS)	ethyl	2,4-difluorophenyl	546
41	trans (RS,RS)	-H	3,4-difluorophenyl	519
42	trans (RS,RS)	isopropyl	3,4-difluorophenyl	560
43	trans (RS,RS)	ethyl	3,4-difluorophenyl	546
44	trans (RS,RS)	-H	4-chloro-2-fluorophenyl	535
45	trans (RS,RS)	isopropyl	4-chloro-2-fluorophenyl	577
46	trans (RS,RS)	ethyl	4-chloro-2-fluorophenyl	562
47	trans (R,R)	-CH ₂ CF ₃	4-chlorophenyl	582
48	trans (R,R)	-CH(CH ₃)CH ₂ CH ₃	4-fluorophenyl	556
49	trans (RS,RS)	-CH ₂ CH ₂ N(CH ₃) ₂	4-chlorophenyl	587

EXAMPLE 50



(±)-trans-3-(4-Chlorophenyl)-4-{[4-cyclohexyl-4-(ethoxycarbonyl)piperidin-1-yl]carbonyl}-1-isopropylpiperidinium trifluoroacetate

5 Step A: Preparation of 4-(ethoxycarbonyl)-3-oxopiperidinium chloride

A mixture of ethyl 1-benzyl-3-oxopiperidine-4-carboxylate hydrochloride (20.0 g, 67.0 mmol) and 10% Pd/C (2.00 g; Degussa Type E101) in ethanol/water (1:1; 300 mL) was hydrogenated at 50 psi for 4 h. The resulting mixture was filtered through celite® and the filtrate evaporated *in vacuo* to give the
10 title compound as a brown solid (67.0 mmol).

Step B: Preparation of 1-tert-butyl 4-ethyl 3-oxopiperidine-1,4-dicarboxylate

Di-tert-butyl-dicarbonate (17.5 g, 80.4 mmol) was added in one portion to a stirred mixture of the crude product of step A (67.0 mmol), sodium
15 bicarbonate (6.20 g, 73.7 mmol) and sodium chloride (11.7 g, 201 mmol) in water/chloroform (1:2; 300 mL) and the resulting mixture heated at 60°C for 3 h. After cooling to room temperature, the organic phase was separated and the aqueous phase extracted three times with chloroform. The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The crude residue
20 (27.1 g) was used without further purification in the subsequent reaction.

Step C: Preparation of 1-tert-butyl 4-ethyl 5-[[trifluoromethyl)sulfonyl]oxy]-3,6-dihydropyridine-1,4(2H)-dicarboxylate

Trifluoromethanesulfonic anhydride (12.4 mL, 73.7 mmol) was added
25 over approximately 0.1 h, *via* syringe, to a stirred solution of the product of step B (27.1 g, 67.0 mmol) and *N,N*-diisopropylethylamine (14.0 mL, 80.4 mmol) in

methylen chloride (250 mL) at -78°C. After allowing to warm to ambient temperature overnight, the reaction mixture was quenched with saturated aqueous sodium bicarbonate, poured into water and extracted three times with methylene chloride. The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (gradient elution; 0-20% ethyl acetate/hexanes as eluent) afforded the title compound as an amber colored oil (17.6 g).

10 Step D: Preparation of 1-*tert*-butyl 3-ethyl 4-(4-chlorophenyl)-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate

A vigorously stirred suspension of the product of step C (1.00 g, 2.48 mmol), 4-chlorophenylboronic acid (0.427 g, 2.73 mmol) and [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) (0.102 g, 0.124 mmol) in toluene/ethanol (3:2; 24.0 mL) was degassed *via* three vacuum/nitrogen ingress cycles and then heated to approximately 80°C. Aqueous 2 M sodium carbonate (3.10 mL, 6.20 mmol) was added dropwise *via* syringe and the resulting mixture maintained at reflux overnight. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and filtered through celite[®]. The filtrate was poured into water and extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by medium pressure liquid chromatography on silica gel (gradient elution; 0-15% ethyl acetate/hexanes as eluent) furnished the title compound as a colorless oil (0.828 g).

25 Step E: Preparation of (±)-1-*tert*-butyl 3-ethyl 4-(4-chloro-phenyl)piperidine-1,3-dicarboxylate

Magnesium metal (1.23 g, 51.0 mmol) was added in three portions over approximately 0.3 h to a stirred solution of the product of step D (1.85 g, 5.1 mmol) in methanol (40 mL) at ambient temperature. After stirring overnight, the reaction mixture was poured into 1 N hydrochloric acid (100 mL) and extracted three times with ethyl acetate. The combined organic extracts were washed with saturated sodium bicarbonate, brine, dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by medium pressure liquid chromatography on silica gel (gradient elution; 0-25% ethyl acetate/hexanes as eluent) provided the title compound (mixture of *cis/trans* diastereoisomers) as a colorless oil (1.5 g).

Step F: Preparation of (\pm)-*trans*-1-(*tert*-butoxycarbonyl)-3-(4-chlorophenyl)piperidine-4-carboxylic acid

Excess sodium metal was added to a stirred solution of the product of step E (1.5 g, 4.1 mmol) in methanol (20 mL) at ambient temperature, and the resulting solution heated to 75°C. After approximately 1 h, 5 M sodium hydroxide (5.0 mL) was added and the reaction mixture heated to 100°C for an additional hour. After cooling to room temperature, the reaction mixture was acidified to pH 5 with 2 N hydrochloric acid and extracted three times with methylene chloride. The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated *in vacuo*, to give the title compound as a colorless solid (1.3 g). The crude product was used without further purification in the subsequent reaction.

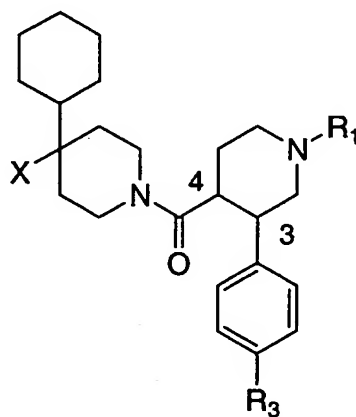
Step G: Preparation of (\pm)-*trans*-3-(4-chlorophenyl)-4-{[4-cyclohexyl-4-(ethoxycarbonyl)piperidin-1-yl]carbonyl}piperidinium trifluoroacetate

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.034 g, 0.177 mmol) was added to a stirred mixture of the crude product of step F (0.040 g, 0.118 mmol), 4-cyclohexyl-4-(ethoxycarbonyl)piperidinium chloride (0.049 g, 0.177 mmol), 1-hydroxybenzotriazole (0.024 g, 0.177 mmol) and *N*-methylmorpholine (0.020 mL, 0.177 mmol) in methylene chloride (0.5 mL) at ambient temperature. After approximately 18 h, the reaction mixture was poured into water/saturated sodium bicarbonate (1:1) and extracted three times with methylene chloride. The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated *in vacuo*. A saturated solution of hydrochloric acid in ethyl acetate (1.0 mL) was added to a solution of the crude amide in methylene chloride (1.0 mL) at room temperature. After 18 h, the volatiles were evaporated *in vacuo*, and the crude residue purified by preparative reversed phase high pressure liquid chromatography on YMC Pack Pro C18 phase (gradient elution; 0-100% acetonitrile/water as eluent, 0.1% TFA as modifier) to give the title compound (0.034 g) as an off-white solid [MS: *m/z* 461 (MH⁺)].

Step H: Preparation of (\pm)-*trans*-3-(4-chlorophenyl)-4-{[4-cyclohexyl-4-(ethoxycarbonyl)piperidin-1-yl]carbonyl}-1-isopropylpiperidinium trifluoroacetate

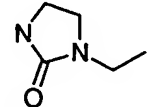
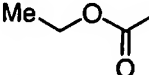
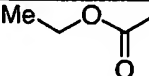
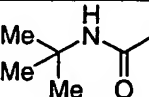
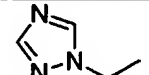
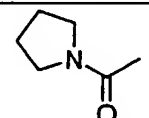
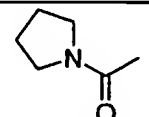
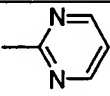
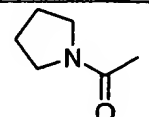
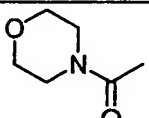
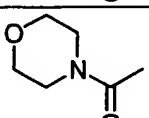
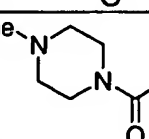
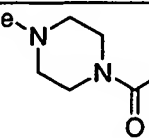
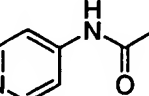
- Sodium triacetoxyborohydride (34.5 mg, 0.163 mmol) was added to a stirred solution of the product of step G (25.0 mg, 54.2 mmol), acetone (23.9 mL, 0.325 mmol) and acetic acid (9.3 mL, 0.163 mmol) in methylene chloride (0.5 mL) at ambient temperature. After 18 h, the reaction mixture was poured into saturated aqueous sodium bicarbonate and extracted three times with methylene chloride. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by preparative reversed phase high pressure liquid chromatography on YMC Pack Pro C18 phase (gradient elution; 0-100% acetonitrile/water as eluent, 0.1% TFA as modifier) afforded the title compound as an off-white solid [MS: m/z 503 (MH^+)].

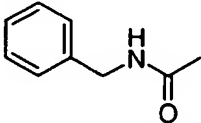
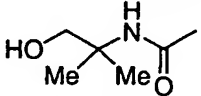
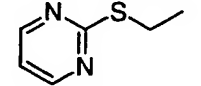
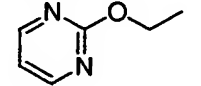
Following a procedure similar to that described above for Example 50, the following compounds can be prepared:

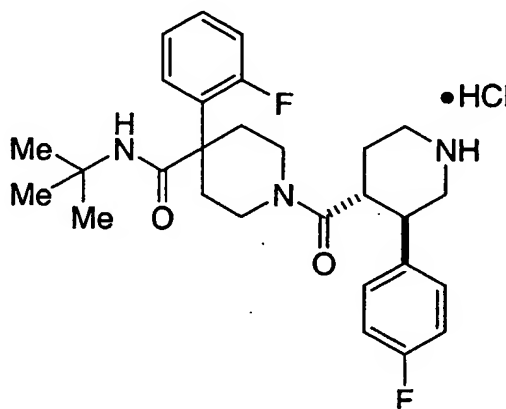


Ex. #	Relativestereo. (3,4)	R ₁	R ₃	X	Parent Ion <i>m/z</i>
51	trans (RS,RS)	-H	-F		472
52	trans (R,R)	-H	-F		472
53	trans (RS,RS)	-H	-Cl		488
54	trans (RS,RS)	-H	-F		445

55	trans (S,S)	-H	-F		445
56	trans (R,R)	-H	-F		445
57	trans (RS,RS)	-H	-F		461
58	trans (RS,RS)	-H	-F		493
59	trans (RS,RS)	-H	-F		454
60	trans (R,R)	-H	-F		454
61	trans (RS,RS)	-H	-Cl		470
62	trans (R,R)	-H	-F		486
63	trans (RS,RS)	-H	-Cl		538
64	trans (RS,RS)	methyl	-Cl		
65	trans (RS,RS)	-H	-H		427
66	trans (R,R)	isopropyl	-F		487
67	trans (RS,RS)	isopropyl	-Cl		530
68	trans (R,R)	isopropyl	-F		514
69	trans (R,R)	isopropyl	-F		496

70	trans (S,S)	-H	-F		471
71	trans (RS,RS)	-H	-Cl		461
72	trans (RS,RS)	-H	-CF ₃		495
73	trans (RS,RS)	-H	-CF ₃		522
74	trans (RS,RS)	-H	-CF ₃		504
75	trans (R,R)	-H	-F		470
76	trans (RS,RS)	-H	-Cl		486
77	trans (R,R)		-F		548
78	trans (R,R)	-H	-F		486
79	trans (RS,RS)	-H	-Cl		502
80	trans (R,R)	-H	-F		499
81	trans (RS,RS)	-H	-Cl		515
82	trans (R,R)	-H	-F		493

83	trans (R,R)	-H	-F		507
84	trans (R,R)	-H	-F		488
85	trans (RS,RS)	-H	-F		497
86	trans (RS,RS)	-H	-F		481

EXAMPLE 87

5 (3R,4R)-4-([4-[(*Tert*-butylamino)carbonyl]-4-(2-fluorophenyl)piperidin-1-yl]carbonyl)-3-(4-fluorophenyl)piperidinium chloride

Step A: Preparation of 4-(2-fluorophenyl)-1-methylpiperidine-4-carbonitrile

N-Methyl-bis-(2'-chloroethyl)amine hydrochloride (8.36 g; 43.1 mmol) was suspended in 60 mL of methylene chloride followed by the addition of 1 eq. of triethylamine (6.0 mL). After 45 min, the mixture was filtered on a medium-pore fritted Buchner funnel to remove the triethylammonium chloride salt. The filtrate was concentrated *in vacuo* resulting in the precipitation of additional salt. The filtration was repeated 2 more times to provide pure *N*-methyl-bis-(2'-chloroethyl)amine. The amine was combined with (2-fluorophenyl)acetonitrile (8.01 g; 43.1 mmol) and tetra-*n*-butylammonium sulfate (1.46 g; 4.31 mmol) followed by the addition of toluene (15

mL). To this solution was added 12.5 N sodium hydroxide dropwise over 10 min. The reaction mixture was heated to 75°C until the starting material had been consumed, poured into H₂O (100 mL) and extracted three times with 200 mL methylene chloride. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude residue was purified on silica gel by first elution with 50:50 ethyl acetate/hexanes followed by 95:5 methylene chloride/methanol (containing 10% v/v ammonium hydroxide) to provide the titled compound

10 Step B: Preparation of 4-carboxy-4-(2-fluorophenyl)-1-methyl-piperidinium chloride

The product of Step A (4.5 g; 20.6 mmol) was heated to 135°C in concentrated hydrochloric acid (25 mL). The volatiles were removed *in vacuo* which provided the crude product. The residue was suspended in toluene (20 mL) and heated under reduced pressure to remove the toluene. This process was repeated three times which furnished the title compound as a powder.

Step C: Preparation of *N*-(*tert*-butyl)-4-(2-fluorophenyl)-1-methyl-piperidine-4-carboxamide

20 To a suspension of the product of the previous step (1.0 g; 3.63 mmol) in methylene chloride (15 mL) was added 4 drops of *N,N*-dimethylformamide and the mixture was cooled to 0°C. A solution of oxalyl chloride (2.0 M in methylene chloride; 1.25 eq; 2.27 mL) was added dropwise over 10 min. After an additional 30 min at 0°C, the reaction mixture was allowed to warm to ambient temperature for 2 h at which time *tert*-butyl amine (5 eq.; 1.92 mL) was added dropwise. The resultant mixture was maintained at room temperature for 18 h and then quenched with a saturated solution of sodium bicarbonate. The aqueous layer was extracted three times with methylene chloride. The combined extracts were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude residue was purified on silica gel and eluted with 95:5 methylene chloride/methanol (containing 10% v/v ammonium hydroxide) which provided 550 mg of the title compound.

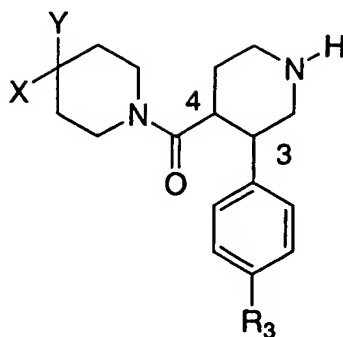
Step D: Preparation of *N*-(*tert*-butyl)-4-(2-fluorophenyl)piperidine-4-carboxamide

To a solution of the product of step C (550 mg; 1.88 mmol) in toluene (10 mL) was added 1-chloroethyl chloroformate (15 mmol; 1.62 mL) and the reaction was heated to reflux for 36 h. The volatiles were removed *in vacuo*, the crude carbamate was then dissolved in methanol (10 mL) and the resultant solution was heated to reflux for 2 h. The volatiles were removed *in vacuo*, the crude amine was dissolved in methylene chloride (100 mL) and the solution was washed with a saturated solution of sodium bicarbonate, brine and the compound dried (Na₂SO₄). The drying agent was removed by filtration and the volatiles were removed *in vacuo* to furnish the crude product which was purified on silica gel using a gradient elution (95:5 then 90:10 methylene chloride/methanol (containing 10% v/v ammonium hydroxide) to afford the title compound.

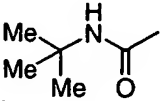
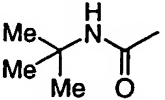
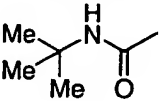
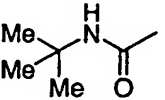
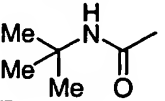
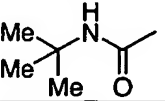
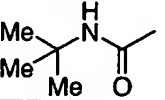
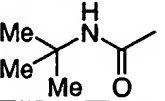
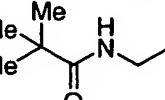
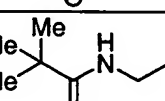
Step E: Preparation of (3*R*,4*R*)-4-{[4-[(*tert*-butylamino)carbonyl]-4-(2-fluorophenyl)piperidin-1-yl]carbonyl}-3-(4-fluorophenyl)-piperidinium chloride

The product of step D (70 mg) was combined with (3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(4-fluorophenyl)piperidine-4-carboxylic acid (0.1971 mmol; 55 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (57 mg) and 1-hydroxybenzotriazole (40 mg) to which methylene chloride (2.5 mL) was added. The reaction mixture was maintained at ambient temperature for 24 h. The reaction mixture was diluted with methylene chloride (100 mL), washed with a saturated solution of sodium bicarbonate, brine and dried (Na₂SO₄). The drying agent was removed by filtration and the volatiles were removed *in vacuo* to furnish the crude *N*-BOC protected product which was purified on silica gel (eluted with 50:50 to 75:25 ethyl acetate:hexane). The *N*-BOC protected product was dissolved in ethyl acetate (2 mL) and a saturated solution of hydrogen chloride in ethyl acetate (2 mL) was added. The reaction mixture was maintained at ambient temperature for 90 min. The volatiles were removed *in vacuo*, the crude product was triturated twice with diethyl ether, and the purified product was dried *in vacuo* to provide 55 mg of the title compound [MS: *m/z* 484 (MH⁺)].

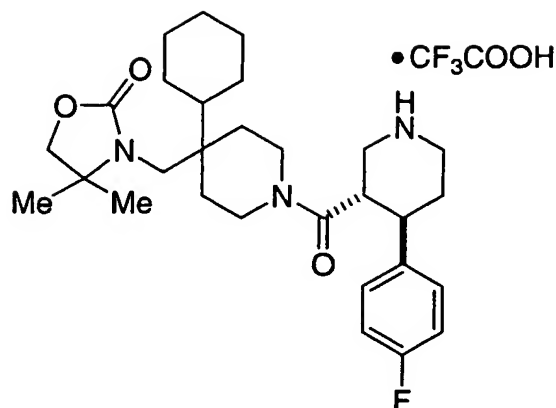
Following a procedure similar to that described above for Example 87, the following compounds were prepared:



Ex. #	Relative stereo. (3,4)	R ³	X	Y	Parent Ion m/z
88	trans (RS,RS)	-F	phenyl	phenyl	443
89	trans (RS,RS)	-F	phenyl	-H	367
90	trans (RS,RS)	-F		-H	381
91	trans (S,S)	-F			439
92	trans (S,S)	-F		-CH ₂ CH=CH ₂	389
93	trans (S,S)	-F		methyl	363
94	trans (S,S)	-F		-H	349
95	trans (S,S)	-F		phenyl	466
96	trans (RS,RS)	-Cl		2-fluorophenyl	500
97	trans (R,R)	-F		2-fluorophenyl	498
98	trans (RS,RS)	-Cl		2-fluorophenyl	514
99	trans (R,R)	-F		4-iodophenyl	592

100	trans (RS,RS)	-Cl		4-iodophenyl	608
101	trans (R,R)	-F		4-(CF ₃)phenyl	534
102	trans (RS,RS)	-Cl		4-(CF ₃)phenyl	550
103	trans (R,R)	-F		4-chlorophenyl	500
104	trans (RS,RS)	-Cl		4-chlorophenyl	516
105	trans (R,R)	-F		3,4-difluorophenyl	502
106	trans (RS,RS)	-Cl		3,4-difluorophenyl	518
107	trans (R,R)	-F		3-chlorophenyl	500
108	trans (RS,RS)	-F		2,4-dichlorophenyl	548
109	trans (RS,RS)	-F		3-methoxyphenyl	510

EXAMPLE 110



(3S,4R)-3-((4-Cyclohexyl-4-[(4,4-dimethyl-2-oxo-1,3-oxazolidin-3-yl)methyl]piperidin-1-yl)carbonyl)-4-(4-fluorophenyl)piperidin-1-ium trifluoroacetate

5 Step A: Preparation of 3-(ethoxycarbonyl)-4-oxopiperidinium chloride

A mixture of ethyl 1-benzyl-4-oxopiperidine-3-carboxylate hydrochloride (25.0 g, 84.0 mmol) and 10% Pd/C (2.5 g Degussa Type E101) in ethanol/water (1:1; 300 mL) was hydrogenated at 50 psi for 4h. The resulting mixture was filtered through celite® and the filtrate evaporated *in vacuo* to give the title
10 compound as a brown solid (84 mmol).

Step B: Preparation of 1-tert-butyl 3-ethyl 4-oxopiperidine-1,3-dicarboxylate

Di-tert-butyl dicarbonate (21.2 g, 97.0 mmol) was added in one portion to a stirred mixture of the crude product of step A (84.0 mmol), sodium bicarbonate (7.7 g, 92.0 mmol) and sodium chloride (14.7 g, 252 mmol) in water/chloroform (1:2; 300 mL) and the resulting mixture heated at 60°C for 3 h. After cooling to room temperature, the organic phase was separated and the aqueous phase extracted three times with chloroform. The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The residue (33.8 g) was used without further
20 purification in the subsequent reaction.

Step C: Preparation of 1-tert-butyl 3-ethyl 4-[[[(trifluoromethyl)-sulfonyl]oxy]-5,6-dihydropyridine-1,3(2H)-dicarboxylate

Trifluoromethanesulfonic anhydride (15.5 mL, 92.0 mmol) was added over approximately 0.1 h, *via* syringe, to a stirred solution of the product of step B (33.8 g, 84.0 mmol) and *N,N*-diisopropylethylamine (17.6 mL, 101.0 mmol) in
25

methylene chloride (300 mL) at -78°C. After allowing to warm to ambient temperature overnight, the reaction mixture was quenched with saturated aqueous sodium bicarbonate, poured into water and extracted three times with methylene chloride. The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (gradient elution; 0-20% ethyl acetate/hexanes as eluent) gave the title compound as an amber colored oil (23.0 g).

10 Step D: Preparation of 1-*tert*-butyl 3-ethyl 4-(4-fluorophenyl)-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate

 A vigorously stirred suspension of the product of step C (1.00 g, 2.48 mmol), 4-fluorophenylboronic acid (0.382 g, 2.73 mmol) and [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) (0.102 g, 0.124 mmol) in toluene/ethanol (3:2; 24.0 mL) was degassed *via* three vacuum/nitrogen ingress cycles and then heated to approximately 80°C. Aqueous 2 M sodium carbonate (3.10 mL, 6.20 mmol) was added dropwise *via* syringe and the resulting mixture maintained at reflux overnight. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and filtered through celite®. The filtrate was poured into water and extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by medium pressure liquid chromatography on silica gel (gradient elution; 0-15% ethyl acetate/hexanes as eluent) afforded the title compound as a colorless oil (0.762 g).

25 Step E: Preparation of 1-*tert*-butyl 3-ethyl 4-(4-fluorophenyl)piperidine-1,3-dicarboxylate

 Magnesium metal (0.525 g, 21.8 mmol) was added in three portions over approximately 0.3 h to a stirred solution of the product of step D (0.762 g, 2.18 mmol) in methanol at ambient temperature. After stirring overnight, the reaction mixture was poured into 1 N hydrochloric acid (100 mL) and extracted three times with ethyl acetate. The combined organic extracts were washed with saturated sodium bicarbonate, brine, dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by medium pressure liquid chromatography on silica gel (gradient elution; 0-25% ethyl acetate/hexanes as eluent) furnished the title compound (3:1 mixture of *cis/trans* diastereoisomers) as a colorless oil (0.651 g).

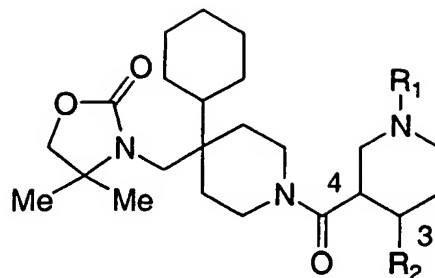
Step F: Preparation of (±)-*trans*-1-(*tert*-butoxycarbonyl)-4-(4-fluorophenyl)piperidine-3-carboxylic acid

Excess sodium metal was added to a stirred solution of the product of step E (0.651 g, 1.85 mmol) in methanol (5.0 mL) at ambient temperature, and the resulting solution was heated to 75°C. After approximately 1 h, 5 M sodium hydroxide (3.0 mL) was added and the reaction mixture heated to 100°C for an additional 1 h. After cooling to room temperature, the reaction mixture was acidified to pH 5 with 2 N hydrochloric acid and extracted three times with methylene chloride. The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The crude product was used without further purification in the subsequent reaction.

Step G: Preparation of (±)-*trans*-3-({4-cyclohexyl-4-[(4,4-dimethyl-2-oxo-1,3-oxazolidin-3-yl)methyl]piperidin-1-yl}carbonyl)-4-(4-fluorophenyl)piperidinium trifluoroacetate

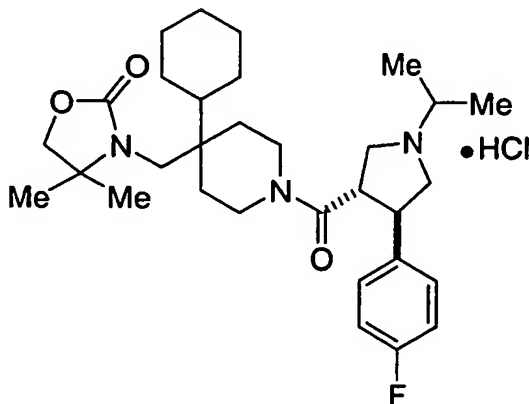
1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.0174 g, 0.091 mmol) was added to a stirred mixture of the crude product of step F (0.0294 g, 0.091 mmol), 4-cyclohexyl-4-[(4,4-dimethyl-2-oxo-1,3-oxazolidin-3-yl)methyl]piperidinium chloride (0.025 g, 0.076 mmol), 1-hydroxybenzotriazole (0.0123 g, 0.091 mmol) and *N*-methylmorpholine (0.010 mL, 0.091 mmol) in methylene chloride (0.500 mL) at ambient temperature. After approximately 18 h, the reaction mixture was poured into water/saturated sodium bicarbonate (1:1) and extracted three times with methylene chloride. The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated *in vacuo*. A saturated solution of hydrogen chloride in ethyl acetate (1.0 mL) was added to a solution of the crude amide in methylene chloride (1.0 mL) at room temperature. After 18 h, the volatiles were evaporated *in vacuo*, and the crude residue purified by preparative reversed phase high pressure liquid chromatography on YMC Pack Pro C18 phase (gradient elution; 0-100% acetonitrile/water as eluent, 0.1% TFA as modifier) to give the title compound (0.031 g) as an off-white solid [MS: *m/z* 500 (MH⁺)].

Following a procedure similar to that described above for Example 110, the following compounds can be prepared:



Ex. #	Relative stereo. (3,4)	R ¹	R ²	Parent Ion <i>m/z</i>
111	trans (RS,RS)	-H	3-chlorophenyl	516
112	trans (RS,RS)	-H	4-methoxyphenyl	512
113	trans (RS,RS)	-H	4-chlorophenyl	516
114	trans (R,R)	methyl	4-fluorophenyl	
115	trans (R,R)	methyl	3-chlorophenyl	
116	trans (R,R)	methyl	4-methoxyphenyl	
117	trans (R,R)	methyl	4-chlorophenyl	
118	trans (R,R)	isopropyl	4-fluorophenyl	
119	trans (R,R)	isopropyl	4-chlorophenyl	
120	trans (R,R)	isopropyl	2,4-difluorophenyl	

EXAMPLE 121



- 5 (3*S*,4*R*)-3-({4-Cyclohexyl-4-[(4,4-dimethyl-2-oxo-1,3-oxazolidin-3-yl)methyl]piperidin-1-yl}carbonyl)-4-(4-fluorophenyl)-1-isopropylpyrrolidinium chloride

Step A: Preparation of (4*S*)-4-benzyl-3-[(2*E*)-3-(4-fluorophenyl)prop-2-enoyl]-1,3-oxazolidin-2-one

A flame-dried 1 L 3-necked flask equipped with a mechanical stirrer was charged with (2*E*)-3-(4-fluorophenyl)prop-2-enoic acid (20.769 g; 0.125 mol) and tetrahydrofuran (275 mL). The reaction was cooled to -20°C followed by the sequential addition of triethylamine (16.443 g; 0.163 mol) and trimethylacetyl chloride (16.580 g; 0.138 mol). After 30 min, the reaction was warmed to ambient temperature where it remained for an additional 90 min. A separate 2 L 3-necked flask, equipped with a mechanical stirrer, and a filter funnel, was charged with (5*S*)-4-benzyl-2-oxazolidinone (20.20 g; 0.114 mol), anhydrous powdered lithium chloride (5.316 g; 0.125 mol), tetrahydrofuran (500 mL) and triethylamine (14.996 g; 0.148 mol) and cooled to -20°C. The mixed anhydride was rapidly added to the oxazolidinone solution through the filter funnel using a slight vacuum. After 30 min, the reaction was allowed to warm to ambient temperature for 5 h. The reaction was filtered through a fritted-funnel and concentrated *in vacuo*. The crude residue was diluted with ethyl acetate, washed with 1 N hydrochloric acid, saturated sodium bicarbonate, brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified on a silica gel chromatography column eluted with methylene chloride. Evaporation of the purified fractions and drying *in vacuo* afforded 26.36 g of the title compound.

Step B: Preparation of (4*S*)-4-benzyl-3-[[[(3*R*,4*R*)-1-benzyl-4-(4-fluorophenyl)pyrrolidin-3-yl]carbonyl]-1,3-oxazolidin-2-one

To a cooled (0°C) solution of the product of step A (12.667 g; 38.9 mmol) in methylene chloride (110 mL) was added *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (13.866 g; 58.4 mmol) followed by a catalytic amount of trifluoroacetic acid (0.15 mL). After 10 min at 0°C, the reaction was allowed to warm to ambient temperature for 8 h. The reaction mixture was diluted with methylene chloride and washed with saturated sodium bicarbonate, brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The crude residue was purified on a silica gel chromatography column eluted with methylene chloride to afford 7.42 g of the less polar diastereoisomer and 7.79 g of the more polar diastereoisomer.

Step C: Preparation of *tert*-butyl (3*R*,4*R*)-3-[[*(4S)*-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl]-4-(4-fluorophenyl)pyrrolidine-1-carboxylate

To a suspension of the product of step B (2.0 g; 4.4 mmol) in toluene (20 mL) was added 4 eq of 1-chloroethyl chloroformate (17.5 mmol; 1.33 mL). The reaction was heated to 100°C for 6 h at which time starting material still remained. Thus, an additional 2 eq. of 1-chloroethyl chloroformate (8.8 mmol; 0.66 mL) was added and heating was resumed for another 20 h. The volatiles were removed *in vacuo* and the crude carbamate was dissolved in methanol (20 mL). The reaction mixture was heated to 70°C for 2 h. The volatiles were removed *in vacuo* and the crude amine was dissolved in methylene chloride (400 mL) followed by washing the organic solution with saturated sodium bicarbonate and brine. The organic phase was dried (Na₂SO₄), filtered and concentrated *in vacuo* to provide the crude amine which was purified on silica gel using a gradient elution (50% ethyl acetate/hexane to elute the starting material followed by 9:1 methylene chloride/methanol (containing 10% v/v ammonium hydroxide). This provided 720 mg of the desired amine. The amine (720 mg; 1.96 mmol) was dissolved in methylene chloride (5 mL) and saturated sodium bicarbonate (5 mL) was added followed by di-*tert*-butyldicarbonate (533 mg; 2.45 mmol). After 1 h, the mixture was diluted with methylene chloride (100 mL) followed by washing the organic solution with saturated sodium bicarbonate and brine. The organic phase was dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified on silica gel (30% ethyl acetate/hexane) which furnished 840 mg of the title compound.

Step D: Preparation of (3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(4-fluorophenyl)pyrrolidine-3-carboxylic acid

To a cooled (0°C) solution of the product of step C (835 mg; 1.78 mmol) lithium hydroxide (85 mg; 3.56 mmol) in 15 mL of a 4:1 mixture of tetrahydrofuran-water was added a 30% aqueous solution of hydrogen peroxide. After 5 min, the solution was warmed to ambient temperature and stirred for 5 h. The reaction mixture was poured into a 10% aqueous solution of sodium sulfite and then acidified to pH 3 with 1 N hydrochloric acid. The aqueous solution was extracted three times with ethyl acetate. The organic phase was washed with brine, dried (MgSO₄), filtered, concentrated *in vacuo* and the crude acid was purified on silica gel (30% ethyl acetate/hexane with 1% acetic acid) which furnished 520 mg of the title compound.

Step E: Preparation of (3*R*,4*R*)-3-({4-cyclohexyl-4-[(4,4-dimethyl-2-oxo-1,3-oxazolidin-3-yl)methyl]piperidin-1-yl}carbonyl)-4-(4-fluorophenyl)pyrrolidinium chloride

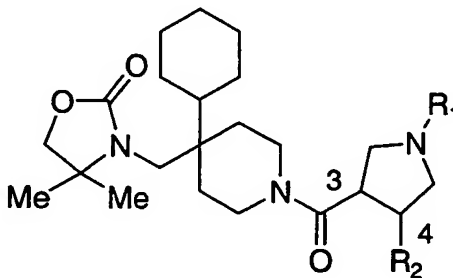
5 To a suspension of 4-cyclohexyl-4-[(4,4-dimethyl-2-oxo-1,3-oxazolidin-3-yl)methyl]piperidinium chloride (150 mg; 0.4532 mmol) in methylene chloride (4.0 mL) was added *N*-methylmorpholine (183 mg; 0.2 mL). After 20 min, the following reagents were added sequentially: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (130 mg; 0.6798 mmol), 1-hydroxybenzotriazole (92
10 mg; 0.6798 mmol) and the product of step D (154 mg; 0.4985 mmol). The final reaction mixture was maintained at ambient temperature for 48 h. The reaction mixture was diluted with methylene chloride (100 mL) followed by washing the organic solution with saturated sodium bicarbonate and brine. The organic phase was dried (Na₂SO₄), filtered and concentrated *in vacuo* to provide the crude *N*-BOC
15 protected pyrrolidine that was purified on silica gel (50% ethyl acetate/hexane as the elution solvent). The crude *N*-BOC protected pyrrolidine was then dissolved in ethyl acetate (2 mL) followed by the addition of a saturated solution of hydrogen chloride in ethyl acetate (2 mL). The reaction mixture was maintained at ambient temperature for 2 h at which time the volatiles were removed *in vacuo*. The crude product was
20 triturated to high purity with diethyl ether which furnished 204 mg of the title compound as a hydrochloride salt.

Step F: Preparation of (3*S*,4*R*)-3-({4-cyclohexyl-4-[(4,4-dimethyl-2-oxo-1,3-oxazolidin-3-yl)methyl]piperidin-1-yl}carbonyl)-4-(4-fluorophenyl)-1-isopropylpyrrolidinium chloride

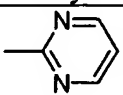
25 A solution of the product of step E (100 mg; 0.1916 mmol) in methylene chloride (100 mL) was converted to the free-base by washing with saturated sodium bicarbonate. The organic phase was washed with brine, dried (Na₂SO₄), filtered and the volatiles were removed *in vacuo*. The residue was
30 dissolved in methylene chloride (2 mL) and cooled to 0°C. Acetone (111 mg; 0.14 mmol) was added, followed by acetic acid (57 mg; 0.9579 mmol) and sodium triacetoxymethylborohydride (0.575 mmol). The reaction mixture was stirred and allowed to warm to room temperature over 36 h at which time the reaction was quenched with saturated sodium bicarbonate. After extracting three times with methylene chloride,
35 the organic solution was washed with brine, dried (Na₂SO₄), filtered and concentrated

- 5 *in vacuo* to provide the crude residue which was purified on silica gel (93:7 methylene chloride/methanol (containing 10% v/v ammonium hydroxide). The product was dissolved in ethyl acetate (2 mL) and converted to the hydrochloride salt by addition of a saturated solution of hydrogen chloride in ethyl acetate (2 mL). The reaction mixture was maintained at ambient temperature for 30 min at which time the volatiles were removed *in vacuo*. The solid was triturated to high purity with diethyl ether which furnished 95 mg of the title compound as the hydrochloride salt [MS: m/z 528 (MH^+)].

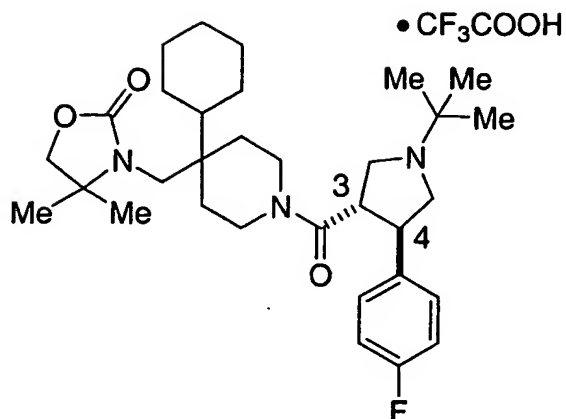
- 10 Following a procedure similar to that described above for Example 121, the following compounds were prepared:



Ex. #	Relative stereo. (3,4)	R1	R2	Parent Ion m/z
122	trans (SR,RS)		4-chlorophenyl	592
123	trans (SR,RS)	-H	4-chlorophenyl	502
124	trans (R,S)	-H	4-chlorophenyl	502
125	trans (R,S)	methyl	4-chlorophenyl	516
126	trans (R,S)	isopropyl	4-chlorophenyl	544
127	trans (S,R)	-H	4-chlorophenyl	502
128	trans (S,R)	methyl	4-chlorophenyl	516
129	trans (S,R)	isopropyl	4-chlorophenyl	544
130	trans (SR,RS)	-H	4-fluorophenyl	486
131	trans (SR,RS)	isopropyl	4-fluorophenyl	528
132	trans (SR,RS)	ethyl	4-fluorophenyl	514
133	trans (SR,RS)	-H	3,4-dichlorophenyl	536
134	trans (SR,RS)	isopropyl	3,4-dichlorophenyl	578

135	trans (S,R)	-H	4-fluorophenyl	486
136	trans (S,R)	ethyl	4-fluorophenyl	514
137	trans (S,R)		4-fluorophenyl	564
138	trans (SR,RS)	-H	3,4-difluorophenyl	504
139	trans (SR,RS)	isopropyl	3,4-difluorophenyl	546
140	trans (SR,RS)	-H	2,4-difluorophenyl	504
141	trans (SR,RS)	isopropyl	2,4-difluorophenyl	546
142	trans (S,R)	-H	2,4-difluorophenyl	504
143	trans (S,R)	isopropyl	2,4-difluorophenyl	546
144	trans (S,R)	ethyl	2,4-difluorophenyl	532
145	trans (S,R)	-CH ₂ C(CH ₃) ₃	2,4-difluorophenyl	574
146	trans (SR,RS)	-H	3-chloro-4-fluorophenyl	520
147	trans (SR,RS)	isopropyl	3-chloro-4-fluorophenyl	562
148	trans (SR,RS)	-H	3,4-difluorophenyl	503
149	trans (SR,RS)	isopropyl	3,4-difluorophenyl	546
150	trans (SR,RS)	-H	2-thiophene	474
151	trans (SR,RS)	isopropyl	2-thiophene	516
152	trans (SR,RS)	-H	2-(3-chloro-thiophene)	508
153	trans (SR,RS)	isopropyl	2-(3-chloro-thiophene)	550

EXAMPLE 154



(±)-trans-1-Tert-butyl-3-({4-cyclohexyl-4-[4-(4,4-dimethyl-2-oxo-1,3-oxazolidin-3-yl)methyl]piperidin-1-yl}carbonyl)-4-(4-fluorophenyl)pyrrolidinium trifluoroacetate

5

Step A: Preparation of *N*-tert-butyl-*N*-(trimethylsilylmethyl)amine

A mixture of *tert*-butylamine (18.0 mL, 171 mmol) and (chloromethyl)trimethylsilane (7.00 g, 57.1 mmol) was heated in a thick-walled glass tube at 200°C overnight. After cooling to ambient temperature, the reaction mixture was poured into 1 N sodium hydroxide and extracted three times with diethyl ether. The combined organic extracts were washed with brine, dried (MgSO₄), and the volatiles evaporated *in vacuo*. Distillation (atmospheric pressure; ~135°C) of the residual liquid gave the title compound as a colorless liquid (7.67 g).

10

Step B: Preparation of *N*-tert-butyl-*N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)amine

N-tert-Butyl-*N*-(trimethylsilylmethyl)amine (8.47 g, 53.1 mmol) was added dropwise, over approximately 30 min, via a pressure equalizing addition funnel to a stirred solution of aqueous formaldehyde (5.98 mL of a 37 wt. % solution in water, 79.7 mmol) at 0°C (ice cooling). After 45 min, methanol (6.45 mL, 159.3 mmol) was added and the resulting solution was saturated with potassium carbonate. After stirring vigorously for approximately 5 h, the aqueous phase was removed. The organic phase was saturated with potassium carbonate and stirred overnight. The reaction mixture was poured into water and extracted three times with diethyl ether.

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The combined organic extracts were washed with brine, dried (MgSO₄) and the

25

volatiles evaporated *in vacuo*. Distillation (high vacuum; ~70°C) of the residual liquid afforded the title compound as a colorless liquid (3.50 g).

Step C: Preparation of methyl (±)-trans-1-*tert*-butyl-4-(4-fluorophenyl)-pyrrolidine-3-carboxylate

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- Trifluoroacetic acid (38.9 mL, 0.505 mmol) was added to a solution of the product of step B (1.03 g, 5.05 mmol) and methyl (2*E*)-3-(4-fluorophenyl)prop-2-enoate (1.00 g, 5.05 mmol) in methylene chloride (10 mL) at ambient temperature. After 18 h, the reaction mixture was poured into saturated aqueous sodium bicarbonate and extracted three times with methylene chloride. The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography on silica gel (gradient elution; 0-9% methanol (containing 10% v/v ammonium hydroxide)/methylene chloride as eluent) furnished the title compound as a colorless liquid (1.06 g).

Step D: Preparation of (±)-trans-1-*tert*-butyl-3-carboxy-4-(4-fluorophenyl)pyrrolidinium chloride

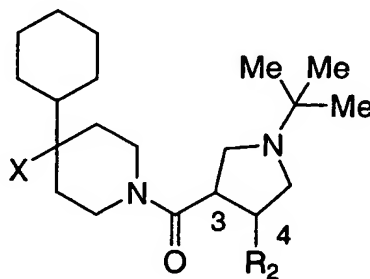
- 20
- A solution of the product of Step C (50.0 mg, 0.179 mmol) in 8 N hydrochloric acid (1.0 mL) was heated at reflux overnight. After cooling to room temperature, the volatiles were evaporated and the residual solid used without further purification in the subsequent reaction.

Step E: Preparation of (±)-trans-1-*tert*-butyl-3-({4-cyclohexyl-4-[(4,4-dimethyl-2-oxo-1,3-oxazolidin-3-yl)methyl]piperidin-1-yl}carbonyl)-4-(4-fluorophenyl)pyrrolidinium trifluoroacetate

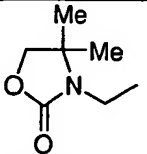
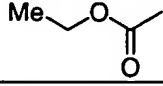
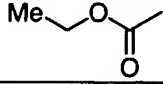
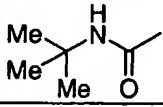
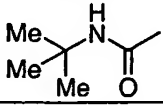
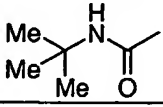
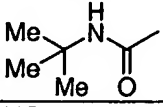
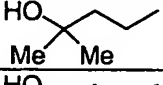
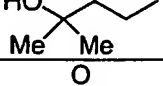
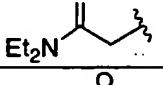
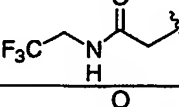
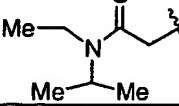
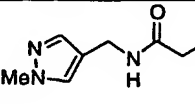
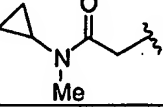
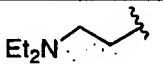
- 25
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35
- 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (51.5 mg, 0.269 mmol) was added to a stirred mixture of 4-cyclohexyl-4-[(4,4-dimethyl-2-oxo-1,3-oxazolidin-3-yl)methyl]piperidinium chloride (54.9 mg, 0.166 mmol), crude product of step D (0.179 mmol), 1-hydroxybenzotriazole (36.3 mg, 0.269 mmol) and *N*-methylmorpholine (59.0 L, 0.537 mmol) in methylene chloride (1.8 mL) at ambient temperature. After approximately 18 h, the reaction mixture was poured into saturated aqueous sodium bicarbonate and extracted three times with methylene chloride. The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated *in vacuo*. Purification of the residue by preparative reversed phase

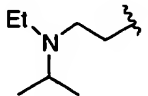
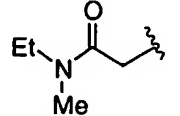
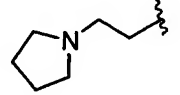
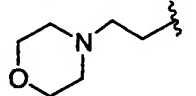
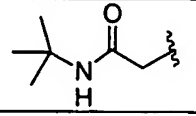
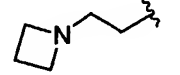
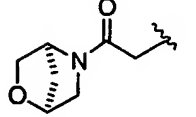
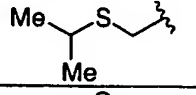
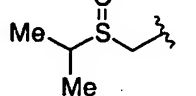
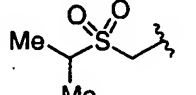
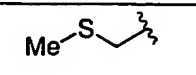
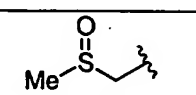
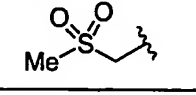
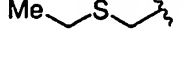
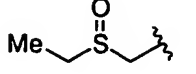
high pressure liquid chromatography on YMC Pack Pro C18 phase (gradient elution; 0-100% acetonitrile/water as eluent, 0.1% TFA as modifier) gave the title compound as an off-white solid [MS: m/z 542 (MH^+)].

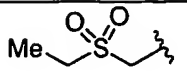
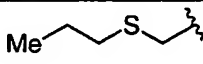
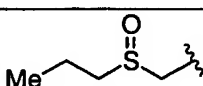
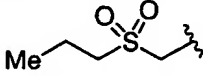
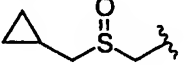
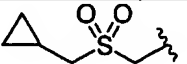
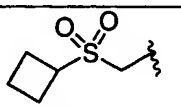
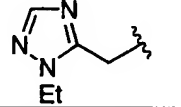
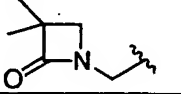
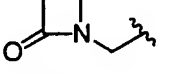
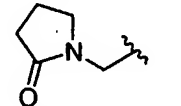
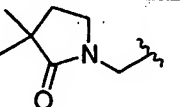
- 5 Following a procedure similar to that described above for Example 154, the following compounds were prepared:



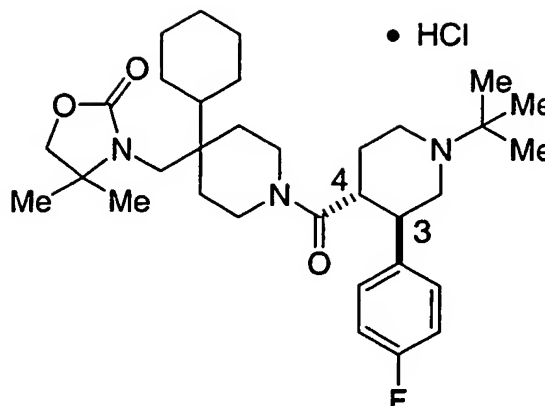
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156	trans (R,S)		2,4-difluorophenyl	560
157	trans (SR,RS)		2,3,4-trifluorophenyl	578
158	trans (SR,RS)		2-chloro-4-fluorophenyl	576
159	trans (SR,RS)		2-iodo-4-fluoro-6-chlorophenyl	686

160	trans (SR,RS)		2,5-difluorophenyl	574
161	trans (SR,RS)		2,4-difluorophenyl	505
162	trans (SR,RS)		4-fluorophenyl	487
163	trans (S,R)		2,4-difluorophenyl	532
164	trans (R,S)		2,4-difluorophenyl	532
165	trans (SR,RS)		2,4-difluorophenyl	532
166	trans (SR,RS)		4-fluorophenyl	514
167	trans (S,R)		2,4-difluorophenyl	519
168	trans (R,S)		2,4-difluorophenyl	519
169	trans (S,R)		2,4-difluorophenyl	546
170	trans (S,R)		2,4-difluorophenyl	572
171	trans (S,R)		2,4-difluorophenyl	560
172	trans (S,R)		2,4-difluorophenyl	584
173	trans (S,R)		2,4-difluorophenyl	544
174	trans (S,R)		2,4-difluorophenyl	532

175	trans (S,R)		2,4-difluorophenyl	546
176	trans (S,R)		2,4-difluorophenyl	532
177	trans (S,R)		2,4-difluorophenyl	530
178	trans (S,R)		2,4-difluorophenyl	546
179	trans (S,R)		2,4-difluorophenyl	546
180	trans (S,R)		2,4-difluorophenyl	516
181	trans (S,R)		2,4-difluorophenyl	572
182	trans (S,R)		2,4-difluorophenyl	521
183	trans (S,R)		2,4-difluorophenyl	537
184	trans (S,R)		2,4-difluorophenyl	553
185	trans (S,R)		2,4-difluorophenyl	493
186	trans (S,R)		2,4-difluorophenyl	509
187	trans (S,R)		2,4-difluorophenyl	525
188	trans (S,R)		2,4-difluorophenyl	507
189	trans (S,R)		2,4-difluorophenyl	523

190	trans (S,R)		2,4-difluorophenyl	539
191	trans (S,R)		2,4-difluorophenyl	521
192	trans (S,R)		2,4-difluorophenyl	537
193	trans (S,R)		2,4-difluorophenyl	553
194	trans (S,R)		2,4-difluorophenyl	549
195	trans (S,R)		2,4-difluorophenyl	565
196	trans (S,R)		2,4-difluorophenyl	565
197	trans (S,R)		2,4-difluorophenyl	542
198	trans (S,R)		2,4-difluorophenyl	544
199	trans (S,R)		2,4-difluorophenyl	516
200	trans (S,R)		2,4-difluorophenyl	530
201	trans (S,R)		2,4-difluorophenyl	558

EXAMPLE 202



(±)-trans-1-Tert-butyl-4-({4-cyclohexyl-4-[(4,4-dimethyl-2-oxo-1,3-oxazolidin-3-yl)methyl]piperidin-1-yl}carbonyl)-3-(2,4-difluorophenyl)piperidinium chloride

5 Step A: Preparation of ethyl 4-(tert-butylamino)butanoate

Ethyl 4-bromobutyrate (20 g; 102.6 mmol) was combined with *tert*-butylamine (37.2 g; 0.514 mol) and heated to 100°C in a sealed tube for 24 h. The contents of the reaction were cooled to ambient temperature, the volatiles were removed *in vacuo* and the crude product was dissolved in 1 N hydrochloric acid. The aqueous layer was extracted twice with diethyl ether and the organic layer discarded. The aqueous layer was adjusted to pH 9 with 2.5 N sodium hydroxide. The aqueous layer was extracted three times with diethyl ether. The combined organic extracts (from the pH 9 aqueous layer) were washed with brine, dried (Na₂SO₄), filtered and the solvent was removed *in vacuo* to afford the title compound (14.2 g).

15

Step B: Preparation of ethyl N-(tert-butyl)-N-(2-ethoxy-2-oxoethyl)-4-aminobutanoate

To a solution of the product of step A (14.2 g; 75.5 mmol) in toluene (150 mL) was added potassium carbonate (20.8 g; 151.1 mmol) and ethyl bromoacetate (18.9 g; 113.3 mmol). The reaction was heated to 120°C for 24 h. The reaction mixture was cooled to ambient temperature and partitioned between 1 N hydrochloric acid and diethyl ether. The aqueous layer was extracted twice with diethyl ether and the organic layer discarded. The aqueous layer was adjusted to pH 9 with 2.5 N sodium hydroxide and extracted three times with diethyl ether. The combined organic extracts (from the pH 9 aqueous layer) were washed with brine,

25

dried (Na_2SO_4), filtered and concentrated *in vacuo* to furnish the title compound (19.2 g).

Step C: Preparation of ethyl 1-*tert*-butyl-3-oxopiperidine-4-carboxylate.

- 5 To a solution of the product of step B (14.0 g; 50.9 mmol) in tetrahydrofuran (200 mL) was added 1.05 eq of potassium *tert*-butoxide (6.0 g; 53.5 mmol). The reaction was maintained at ambient temperature for 2 h and then quenched with a sufficient amount of saturated aqueous ammonium chloride to make the solution pH 8. The tetrahydrofuran was removed *in vacuo* and the aqueous layer
10 was extracted three times with diethyl ether. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound (7.15 g).

Step D: Preparation of ethyl 1-*tert*-butyl-5-[[trifluoromethyl)sulfonyl]-oxy]-1,2,3,6-tetrahydropyridine-4-carboxylate

- 15 To a cooled (-78°C) solution of the product of step C (7.15 g; 31.2 mmol) in methylene chloride (100 mL) was added diisopropylethylamine (5.04 g; 39.0 mmol). Triflic anhydride (9.69g; 34.3 mmol) was then added dropwise over 10 min and the reaction mixture was allowed to warm to ambient temperature over 16 h.
20 The mixture was concentrated to about 50% of the initial volume and directly loaded onto silica gel eluted with 50% ethyl acetate/hexane. Evaporation of the purified fractions provided 5.05 g of the title compound.

Step E: Preparation of ethyl 1-*tert*-butyl-5-(2,4-difluorophenyl)-1,2,3,6-tetrahydropyridine-4-carboxylate

- 25 The product of step D (5.05 g; 14.4 mmol), 2,4-difluorophenylboronic acid (2.85 g; 18.0 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.589 g; 0.7 mmol) were combined and dissolved a 2:1 mixture of toluene:ethanol (54 mL). The reaction was heated to 80°C followed by the dropwise
30 addition of 2 M aqueous sodium carbonate over 10 min. The reaction was maintained at 80°C for 2 h. The reaction was quenched with saturated aqueous sodium bicarbonate and the aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered concentrated *in vacuo*. The crude residue was purified on silica gel using a gradient

elution (30%→40%→60% ethyl acetate/hexane) which furnished the title compound (2.8 g).

Step F: Preparation of methyl (±)-*trans*-1-*tert*-butyl-3-(2,4-difluorophenyl)piperidine-4-carboxylate

5

The product of step E (1 g; 3.1 mmol) was dissolved in ethanol (20 mL) and treated with acetic acid (280 mg; 4.6 mmol) and 20% palladium hydroxide on carbon catalyst (0.760 g). The reaction mixture was stirred for 24 h under 1 atmosphere of hydrogen gas. The reaction was filtered through celite® and the filter cake was rinsed with copious amounts of methanol. The solvents were evaporated and the crude residue was dissolved in methylene chloride. The organic solution was washed with saturated sodium bicarbonate, brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude residue was purified on silica gel using 10% methanol/methylene chloride to provide predominantly the *cis*-disubstituted piperidine. The *cis* isomer, accumulated from several experiments as described above, (5.5 g; 17.0 mmol) was dissolved in methanol (75 mL) followed by the addition of freshly cut sodium metal (1.27 g; 55.3 mmol). The reaction mixture was heated to 70°C for 12 h. The reaction was quenched with saturated aqueous ammonium chloride and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude residue was purified on silica gel (50% ethyl acetate/hexane) which furnished the title compound.

10

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Step G: Preparation of (±)-*trans*-1-*tert*-butyl-4-carboxy-3-(2,4-difluorophenyl)piperidinium chloride

25

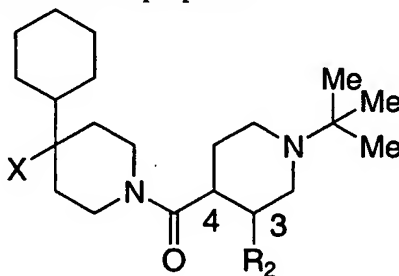
The product of step F (160 mg; 0.515 mmol) was heated to 100°C in concentrated hydrochloric acid for 16 h. The volatiles were removed *in vacuo* and the crude residue was suspended in toluene and evaporated to dryness. This process was repeated three times to provide 170 mg of the title compound.

30

Step H: Preparation of (±)-*trans*-1-*tert*-butyl-4-({4-cyclohexyl-4-[(4,4-dimethyl-2-oxo-1,3-oxazolidin-3-yl)methyl]piperidin-1-yl}carbonyl)-3-(2,4-difluorophenyl)piperidinium chloride

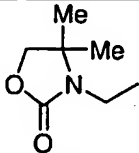
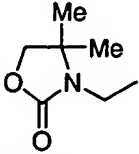
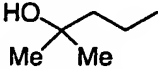
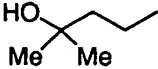
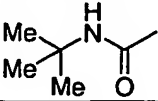
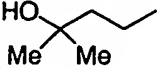
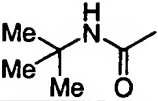
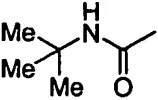
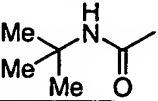
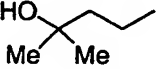
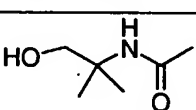
To a suspension of 4-cyclohexyl-4-[(4,4-dimethyl-2-oxo-1,3-oxazolidin-3-yl)methyl]piperidinium chloride (45 mg; 0.136 mmol) in methylene chloride (2.0 mL) was added *N*-methylmorpholine (35 mg; 0.036 mL). A separate flask was charged with the product of step G (50 mg; 0.1497 mmol), methylene chloride (2.0 mL), and *N*-methylmorpholine (35 mg; 0.036 mL) was added. After 20 min, the following reagents were added sequentially to the flask containing the product of step G: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (39 mg; 0.204 mmol), 1-hydroxybenzotriazole (28 mg; 0.204 mmol) followed by the dropwise addition of the piperidine solution from the first flask. The final reaction mixture was maintained at ambient temperature for 48 h. The reaction was diluted with methylene chloride (100 mL) then washed with saturated sodium bicarbonate and brine. The mixture was dried (Na₂SO₄), filtered and concentrated *in vacuo* to provide a crude product that was purified on silica gel (eluted first with 75% ethyl acetate/hexane followed by 95:5 methylene chloride/methanol (containing 10% v/v ammonium hydroxide)). The purified product was dissolved in ethyl acetate (2 mL) and converted to the hydrochloride salt by treatment with a saturated solution of hydrogen chloride in ethyl acetate (2 mL). The reaction mixture was maintained at ambient temperature for 1 h at which time the volatiles were removed *in vacuo*. The crude hydrochloride salt was triturated to high purity with diethyl ether which furnished 50 mg of the title compound [MS: *m/z* 574 (MH⁺)].

Following a procedure similar to that described above for Example 202, the following compounds can be prepared:

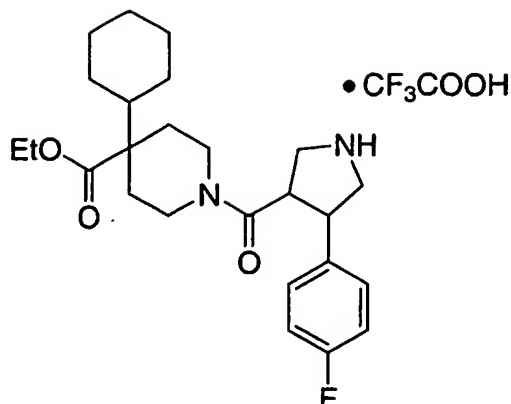


25

Ex. #	Relative stereo. (3,4)	X	R ²	Parent Ion <i>m/z</i>

203	trans (S,S)		2,4-difluorophenyl	575
204	trans (R,R)		2,4-difluorophenyl	575
205	trans (S,S)		2,4-difluorophenyl	
206	trans (R,R)		2,4-difluorophenyl	
207	trans (S,S)		2-fluorophenyl	
208	trans (S,S)		2-fluorophenyl	
209	trans (S,S)		2,4-difluorophenyl	547
210	trans (R,R)		2,4-difluorophenyl	547
211	trans (R,R)		2-fluorophenyl	
212	trans (R,R)		2-fluorophenyl	
213	trans (R,R)		2,4-difluorophenyl	563

EXAMPLE 214



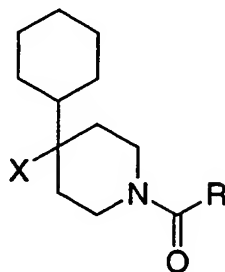
(±)-3-([4-Cyclohexyl-4-(ethoxycarbonyl)piperidin-1-yl]carbonyl)-2-phenylpyrrolidinium trifluoroacetate

- 5 Step A: Preparation of ethyl (±)-1-([1-(*tert*-butoxycarbonyl)-2-phenylpyrrolidin-3-yl]carbonyl)-4-cyclohexylpiperidine-4-carboxylate
- 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.09 mL of a 0.25 M solution in methylene chloride, 0.272 mmol) was added to a stirred mixture of 4-cyclohexyl-4-(ethoxycarbonyl)piperidinium chloride (50.0 mg, 0.181 mmol), (±)-1-(*tert*-butoxycarbonyl)-2-phenylpyrrolidine-3-carboxylic acid (68.6 mg, 0.235 mmol), 1-hydroxybenzotriazole (36.7 mg, 0.272 mmol) and *N*-methylmorpholine (59.7 μ L, 0.543 mmol) in methylene chloride (0.7 mL) at ambient temperature. After approximately 18 h, the reaction mixture was poured into saturated aqueous sodium bicarbonate and extracted three times with methylene chloride. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was used without further purification in the subsequent reaction.

- 20 Step B: Preparation of (±)-3-([4-cyclohexyl-4-(ethoxycarbonyl)piperidin-1-yl]carbonyl)-2-phenylpyrrolidinium chloride
- A saturated solution of hydrogen chloride in ethyl acetate (2.0 mL) was added to a solution of the crude product of step A in methylene chloride (1.0 mL) at room temperature. After 18 h, the volatiles were evaporated *in vacuo*, and the crude residue purified by preparative reversed phase high pressure liquid chromatography on YMC Pack Pro C18 phase (gradient elution; 0-100% acetonitrile/water as eluent, 0.1% TFA as modifier) to give the title compound (59.1 mg) as an off-white solid

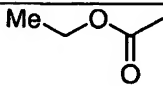
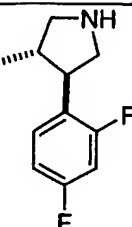
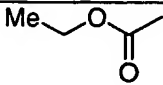
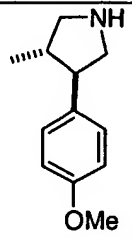
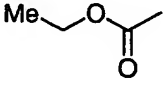
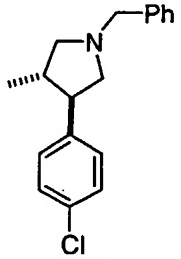
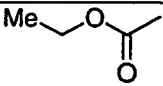
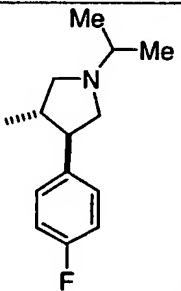
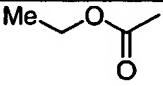
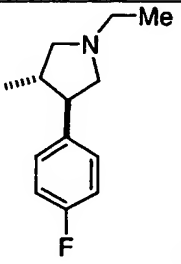
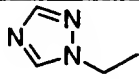
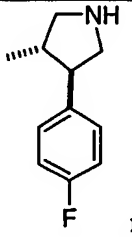
[MS: m/z 413 (MH^+)].

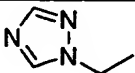
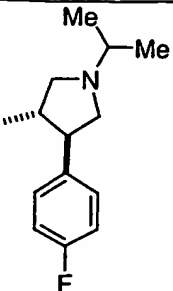
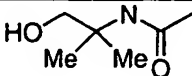
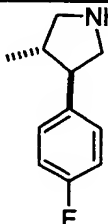
Following a procedure similar to that described above for Example 214, the following compounds were prepared:



5

Ex. #	X	R	Parent Ion m/z
215			413
216			427
217			427
218			431

219		 racemic	449
220		 OMe racemic	443
221		 Cl racemic	537
222		 F racemic	473
223		 F racemic	459
224		 F racemic	440

225		 racemic	482
226			474

BIOLOGICAL ASSAYS

A. Binding Assay. The membrane binding assay was used to identify competitive inhibitors of ^{125}I -NDP-alpha-MSH binding to cloned human MCRs expressed in mouse L- or Chinese hamster ovary (CHO)-cells.

Cell lines expressing melanocortin receptors were grown in T-180 flasks containing selective medium of the composition: 1 L Dulbecco's modified Eagles Medium (DMEM) with 4.5 g L-glucose, 25 mM Hepes, without sodium pyruvate, (Gibco/BRL); 100 ml 10% heat-inactivated fetal bovine serum (Sigma); 10 mL 10,000 unit/mL penicillin & 10,000 $\mu\text{g/mL}$ streptomycin (Gibco/BRL); 10 ml 200 mM L-glutamine (Gibco/BRL); 1 mg/mL geneticin (G418) (Gibco/BRL). The cells were grown at 37°C with CO₂ and humidity control until the desired cell density and cell number was obtained.

The medium was poured off and 10 mls/monolayer of enzyme-free dissociation media (Specialty Media Inc.) was added. The cells were incubated at 37°C for 10 min or until cells sloughed off when flask was banged against hand.

The cells were harvested into 200 mL centrifuge tubes and spun at 1000 rpm, 4° C, for 10 min. The supernatant was discarded and the cells were resuspended in 5 mls/monolayer membrane preparation buffer having the composition: 10 mM Tris pH 7.2-7.4; 4 $\mu\text{g/mL}$ Leupeptin (Sigma); 10 μM Phosphoramidon (Boehringer Mannheim); 40 $\mu\text{g/mL}$ Bacitracin (Sigma); 5 $\mu\text{g/mL}$

Aprotinin (Sigma); 10 mM Pefabloc (Boehringer Mannheim). The cells were homogenized with motor-driven dounce (Talboy setting 40), using 10 strokes and the homogenate centrifuged at 6,000 rpm, 4°C, for 15 min.

The pellets were resuspended in 0.2 mls/monolayer membrane prep
5 buffer and aliquots were placed in tubes (500-1000 µL/tube) and quick frozen in liquid nitrogen and then stored at -80°C.

Test compounds or unlabelled NDP-α-MSH was added to 100 µL of membrane binding buffer to a final concentration of 1 µM. The membrane binding buffer had the composition: 50 mM Tris pH 7.2; 2 mM CaCl₂; 1 mM MgCl₂; 5 mM
10 KCl; 0.2% BSA; 4 µg/mL Leupeptin (SIGMA); 10 µM Phosphoramidon (Boehringer Mannheim); 40 µg/mL Bacitracin (SIGMA); 5 µg/mL Aprotinin (SIGMA); and 10 mM Pefabloc (Boehringer Mannheim). One hundred µL of membrane binding buffer containing 10-40 µg membrane protein was added, followed by 100 µM 125I-NDP-α-MSH to final concentration of 100 pM. The resulting mixture was vortexed briefly
15 and incubated for 90-120 min at room temp while shaking.

The mixture was filtered with Packard Microplate 196 filter apparatus using Packard Unifilter 96-well GF/C filter with 0.1% polyethyleneimine (Sigma). The filter was washed (5 times with a total of 10 mL per well) with room temperature of filter wash having the composition: 50 mM Tris-HCl pH 7.2 and 20 mM NaCl.
20 The filter was dried, and the bottom sealed and 50 µL of Packard Microscint-20 was added to each well. The top was sealed and the radioactivity quantitated in a Packard Topcount Microplate Scintillation counter.

B. Functional assay. Functional cell based assays were developed to discriminate
25 melanocortin receptor agonists from antagonists.

Cells (for example, CHO- or L-cells or other eukaryotic cells) expressing a human melanocortin receptor (see e.g. Yang-YK; Ollmann-MM; Wilson-BD; Dickinson-C; Yamada-T; Barsh-GS; Gantz-I; Mol-Endocrinol. 1997 Mar; 11(3): 274-80) were dissociated from tissue culture flasks by rinsing with Ca and Mg free
30 phosphate buffered saline (14190-136, Life Technologies, Gaithersburg, MD) and detached following 5 min incubation at 37°C with enzyme free dissociation buffer (S-014-B, Specialty Media, Lavellette, NJ). Cells were collected by centrifugation and resuspended in Earle's Balanced Salt Solution (14015-069, Life Technologies, Gaithersburg, MD) with additions of 10 mM HEPES pH 7.5, 5 mM MgCl₂, 1 mM
35 glutamine and 1 mg/ml bovine serum albumin. Cells were counted and diluted to 1 to

5 x 10⁶/mL. The phosphodiesterase inhibitor 3-isobutyl-1-methylxanthine was added to cells to 0.6 mM.

Test compounds were diluted in dimethylsulfoxide (DMSO) (10⁻⁵ to 10⁻¹⁰ M) and 0.1 volume of compound solution was added to 0.9 volumes of cell suspension; the final DMSO concentration was 1%. After room temperature incubation for 45 min, cells were lysed by incubation at 100°C for 5 min to release accumulated cAMP.

cAMP was measured in an aliquot of the cell lysate with the Amersham (Arlington Heights, IL) cAMP detection assay (RPA556). The amount of cAMP production which resulted from an unknown compound was compared to that amount of cAMP produced in response to alpha-MSH which was defined as a 100 % agonist. The EC₅₀ is defined as the compound concentration which results in half maximal stimulation, when compared to its own maximal level of stimulation.

Antagonist assay: Antagonist activity was defined as the ability of a compound to block cAMP production in response to alpha-MSH. Solution of test compounds and suspension of receptor containing cells were prepared and mixed as described above; the mixture was incubated for 15 min, and an EC₅₀ dose (approximately 10 nM alpha-MSH) was added to the cells. The assay was terminated at 45 min and cAMP quantitated as above. Percent inhibition was determined by comparing the amount of cAMP produced in the presence to that produced in the absence of test compound.

C. In vivo food intake models.

1) Overnight food intake. Sprague Dawley rats are injected intracerebroventricularly with a test compound in 400 nL of 50% propylene glycol/artificial cerebrospinal fluid one hour prior to onset of dark cycle (12 hours). Food intake is determined using a computerized system in which each rat's food is placed on a computer monitored balance. Cumulative food intake for 16 h post compound administration is measured.

2) Food intake in diet induced obese mice. Male C57/B16J mice maintained on a high fat diet (60% fat calories) for 6.5 months from 4 weeks of age are dosed intraperitoneally with test compound. Food intake and body weight are measured over an eight day period. Biochemical parameters relating to obesity,

including leptin, insulin, triglyceride, free fatty acid, cholesterol and serum glucose levels are determined.

D. Rat Ex Copula Assay

- 5 Sexually mature male Caesarian Derived Sprague Dawley (CD) rats (over 60 days old) are used with the suspensory ligament surgically removed to prevent retraction of the penis back into the penile sheath during the ex copula evaluations. Animals receive food and water *ad lib* and are kept on a normal light/dark cycle. Studies are conducted during the light cycle.
- 10 1) Conditioning to Supine Restraint for Ex Copula Reflex Tests. This conditioning takes ~ 4 days. Day 1, the animals are placed in a darkened restrainer and left for 15 - 30 minutes. Day 2, the animals are restrained in a supine position in the restrainer for 15 - 30 minutes. Day 3, the animals are restrained in the supine position with the penile sheath retracted for 15 - 30 minutes. Day 4, the animals are restrained
- 15 in the supine position with the penile sheath retracted until penile responses are observed. Some animals require additional days of conditioning before they are completely acclimated to the procedures; non-responders are removed from further evaluation. After any handling or evaluation animals are given a treat to ensure positive reinforcement.
- 20 2) Ex Copula Reflex Tests. Rats are gently restrained in a supine position with their anterior torso placed inside a cylinder of adequate size to allow for normal head and paw grooming. For a 400-500 gram rat, the diameter of the cylinder is approximately 8 cm. The lower torso and hind limbs are restrained with a non-adhesive material (vetrap). An additional piece of vetrap with a hole in it, through
- 25 which the glans penis will be passed, is fastened over the animal to maintain the preputial sheath in a retracted position. Penile responses will be observed, typically termed *ex copula* genital reflex tests. Typically, a series of penile erections will occur spontaneously within a few minutes after sheath retraction. The types of normal reflexogenic erectile responses include elongation, engorgement, cup and flip. An elongation is classified as an extension of the penile body. Engorgement is a dilation of the glans penis. A cup is defined as an intense erection where the distal margin of the glans penis momentarily flares open to form a cup. A flip is a dorsiflexion of the
- 30 penile body.

Baseline and or vehicle evaluations are conducted to determine how
35 and if an animal will respond. Some animals have a long duration until the first

response while others are non-responders altogether. During this baseline evaluation latency to first response, number and type of responses are recorded. The testing time frame is 15 minutes after the first response.

After a minimum of 1 day between evaluations, these same animals are administered the test compound at 20 mg/kg and evaluated for penile reflexes. All evaluations are videotaped and scored later. Data are collected and analyzed using paired 2 tailed t-tests to compared baseline and/ or vehicle evaluations to drug treated evaluations for individual animals. Groups of a minimum of 4 animals are utilized to reduce variability.

Positive reference controls are included in each study to assure the validity of the study. Animals can be dosed by a number of routes of administration depending on the nature of the study to be performed. The routes of administration includes intravenous (IV), intraperitoneal (IP), subcutaneous (SC) and intracerebral ventricular (ICV).

15

E. Models of Female Sexual Dysfunction

Rodent assays relevant to female sexual receptivity include the behavioral model of lordosis and direct observations of copulatory activity. There is also a urethrogenital reflex model in anesthetized spinally transected rats for measuring orgasm in both male and female rats. These and other established animal models of female sexual dysfunction are described in McKenna KE et al, A Model For The Study of Sexual Function In Anesthetized Male And Female Rats, Am. J. Physiol. (Regulatory Integrative Comp. Physiol 30): R1276-R1285, 1991; McKenna KE et al, Modulation By Peripheral Serotonin of The Threshold For Sexual Reflexes In Female Rats, Pharm. Bioch. Behav., 40:151-156, 1991; and Takahashi LK et al, Dual Estradiol Action In The Diencephalon And The Regulation Of Sociosexual Behavior In Female Golden Hamsters, Brain Res., 359:194-207, 1985.

Representative compounds of the present invention were tested and found to bind to the melanocortin-4 receptor. These compounds were generally found to have IC₅₀ values less than 2 μ M. Representative compounds of the present invention were also tested in the functional assay and found generally to activate the melanocortin-4 receptor with EC₅₀ values less than 1 μ M.

35

EXAMPLES OF A PHARMACEUTICAL COMPOSITION

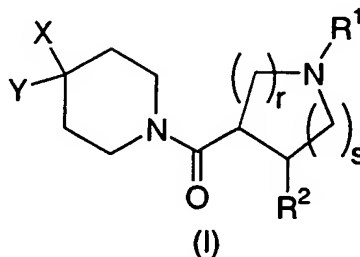
As a specific embodiment of an oral composition of a composition of the present invention, 5 mg of Example 169 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gelatin capsule.

- 5 As another specific embodiment of an oral composition of a compound of the present invention, 10 mg of Example 174 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gelatin capsule.

- 10 While the invention has been described and illustrated in reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred doses as set forth hereinabove may be applicable as a consequence of variations in the responsiveness of the mammal being treated for
- 15 severity of bone disorders caused by resorption, or for other indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected
- 20 variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound of structural formula I:



- 5 or a pharmaceutically acceptable salt thereof;
wherein

r is 1 or 2;

s is 0, 1, or 2;

n is 0, 1 or 2;

10 p is 0, 1, or 2;

R¹ is selected from the group consisting of

hydrogen,

amidino,

15 C₁₋₄ alkyliminoyl,

C₁₋₁₀ alkyl,

(CH₂)_n-C₃₋₇ cycloalkyl,

(CH₂)_n-phenyl,

(CH₂)_n-naphthyl, and

20 (CH₂)_n-heteroaryl wherein heteroaryl is selected from the group consisting of

(1) pyridinyl,

(2) furyl,

(3) thienyl,

(4) pyrrolyl,

25 (5) oxazolyl,

(6) thiazolyl,

(7) imidazolyl,

(8) pyrazolyl,

- 5 (9) isoxazolyl,
 (10) isothiazolyl,
 (11) pyrimidinyl,
 (12) pyrazinyl,
 (13) pyridazinyl,
 (14) quinolyl,
 (15) isoquinolyl,
 (16) benzimidazolyl,
 (17) benzofuryl,
 10 (18) benzothieryl,
 (19) indolyl,
 (20) benzthiazolyl, and
 (21) benzoxazolyl;

15 in which phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R³; and alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R³ and oxo;

- R² is selected from the group consisting of
 20 phenyl,
 naphthyl, and
 heteroaryl wherein heteroaryl is selected from the group consisting of
 (1) pyridinyl,
 (2) furyl,
 25 (3) thienyl,
 (4) pyrrolyl,
 (5) oxazolyl,
 (6) thiazolyl,
 (7) imidazolyl,
 30 (8) pyrazolyl,
 (9) isoxazolyl,
 (10) isothiazolyl,
 (11) pyrimidinyl,
 (12) pyrazinyl,
 35 (13) pyridazinyl,

- (14) quinolyl,
 (15) isoquinolyl,
 (16) benzimidazolyl,
 (17) benzofuryl,
 5 (18) benzothienyl,
 (19) indolyl,
 (20) benzthiazolyl, and
 (21) benzoxazolyl;

in which phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to
 10 three groups independently selected from R³;

R³ is selected from the group consisting of

- C₁₋₆ alkyl,
 (CH₂)_n-phenyl,
 15 (CH₂)_n-naphthyl,
 (CH₂)_n-heteroaryl,
 (CH₂)_n-heterocyclyl,
 (CH₂)_nC₃₋₇ cycloalkyl,
 halogen,
 20 OR⁴,
 (CH₂)_nN(R⁴)₂,
 (CH₂)_nC≡N,
 CO₂R⁴,
 C(R⁴)(R⁴)N(R⁴)₂,
 25 NO₂,
 (CH₂)_nNR⁴SO₂R⁴,
 (CH₂)_nSO₂N(R⁴)₂,
 (CH₂)_nS(O)_pR⁴,
 (CH₂)_nNR⁴C(O)N(R⁴)₂,
 30 (CH₂)_nC(O)N(R⁴)₂,
 (CH₂)_nNR⁴C(O)R⁴,
 (CH₂)_nNR⁴CO₂R⁴,
 CF₃,
 CH₂CF₃,
 35 OCF₃, and

OCH₂CF₃;

- in which heteroaryl is as defined above; phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₄ alkyl, trifluoromethyl, and C₁₋₄ alkoxy; and (CH₂)_n is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄ alkyl;

- each R⁴ is independently selected from the group consisting of
- hydrogen,
 - 10 C₁₋₆ alkyl,
 - (CH₂)_n-phenyl,
 - (CH₂)_n-naphthyl, and
 - (CH₂)_nC₃₋₇ cycloalkyl;

- wherein cycloalkyl is unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, and C₁₋₄ alkoxy;
- 15 or two R⁴ groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC₁₋₄ alkyl;

- 20 each R⁵ is independently selected from the group consisting of
- hydrogen,
 - C₁₋₈ alkyl,
 - (CH₂)_n-phenyl,
 - (CH₂)_n-naphthyl,
 - 25 (CH₂)_n-heteroaryl, and
 - (CH₂)_nC₃₋₇ cycloalkyl;

- wherein heteroaryl is as defined above; phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R³; and alkyl, cycloalkyl, and (CH₂)_n are unsubstituted or substituted with one to three
- 30 groups independently selected from R³ and oxo; or two R⁵ groups together with the atom to which they are attached form a 5- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC₁₋₄ alkyl;

X is selected from the group consisting of

- C₁₋₈ alkyl,
- (CH₂)_nC₃₋₈ cycloalkyl,
- (CH₂)_n-phenyl,
- 5 (CH₂)_n-naphthyl,
- (CH₂)_n-heteroaryl,
- (CH₂)_nheterocyclyl,
- (CH₂)_nC≡N,
- (CH₂)_nCON(R⁵R⁵),
- 10 (CH₂)_nCO₂R⁵,
- (CH₂)_nCOR⁵,
- (CH₂)_nNR⁵C(O)R⁵,
- (CH₂)_nNR⁵CO₂R⁵,
- (CH₂)_nNR⁵C(O)N(R⁵)₂,
- 15 (CH₂)_nNR⁵SO₂R⁵,
- (CH₂)_nS(O)_pR⁵,
- (CH₂)_nSO₂N(R⁵)(R⁵),
- (CH₂)_nOR⁵,
- (CH₂)_nOC(O)R⁵,
- 20 (CH₂)_nOC(O)OR⁵,
- (CH₂)_nOC(O)N(R⁵)₂,
- (CH₂)_nN(R⁵)(R⁵), and
- (CH₂)_nNR⁵SO₂N(R⁵)(R⁵);

wherein heteroaryl is as defined above; phenyl, naphthyl, and heteroaryl are

- 25 unsubstituted or substituted with one to three groups independently selected from R³;
- and alkyl, (CH₂)_n, cycloalkyl, and heterocyclyl are unsubstituted or substituted with
- one to three groups independently selected from R³ and oxo; and

Y is selected from the group consisting of

- 30 C₁₋₈ alkyl,
- C₂₋₆ alkenyl,
- (CH₂)_nC₃₋₈ cycloalkyl,
- (CH₂)_n-phenyl,
- (CH₂)_n-naphthyl,
- 35 (CH₂)_n-heteroaryl, and

(CH₂)_n-heterocyclyl;

wherein heteroaryl is as defined above; phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R³; and alkyl, (CH₂)_n, cycloalkyl, and heterocyclyl are optionally substituted with one to
5 three groups independently selected from R³ and oxo.

2. The compound of Claim 1 wherein R¹ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, (CH₂)₀₋₁C₃₋₆ cycloalkyl, and (CH₂)₀₋₁-phenyl; wherein phenyl is unsubstituted or substituted with one to three
10 groups independently selected from R³; and alkyl and cycloalkyl are optionally substituted with one to three groups independently selected from R³ and oxo.

3. The compound of Claim 1 wherein R² is phenyl or thienyl optionally substituted with one to three groups independently selected from R³.
15

4. The compound of Claim 3 wherein R² is phenyl optionally substituted with one to three groups independently selected from R³.

5. The compound of Claim 1 wherein X is selected from the
20 group consisting of
C₁₋₆ alkyl,
(CH₂)_n-phenyl,
(CH₂)_n-naphthyl,
(CH₂)_n-heteroaryl,
25 (CH₂)_n-heterocyclyl,
(CH₂)_nC(O)N(R⁵)(R⁵),
(CH₂)_nCO₂R⁵,
(CH₂)_nS(O)_pR⁵,
(CH₂)_nOR⁵,
30 (CH₂)_nNR⁵C(O)R⁵, and
(CH₂)_nNR⁵SO₂R⁵;

wherein phenyl, naphthyl, and heteroaryl are optionally substituted with one to three groups independently selected from R³; alkyl and heterocyclyl are optionally substituted with one to three groups independently selected from R³ and oxo; and the

(CH₂)_n group is optionally substituted with one to three groups independently selected from R⁴, halogen, S(O)_pR⁴, N(R⁴)₂, and OR⁴.

6. The compound of Claim 5 wherein X is selected from the group consisting of
- C₁₋₆ alkyl,
 - (CH₂)₀₋₁-phenyl,
 - (CH₂)₀₋₁-heteroaryl,
 - (CH₂)₀₋₁-heterocyclyl,
 - (CH₂)₀₋₁NHC(O)R⁵,
 - (CH₂)₀₋₁CO₂R⁵, and
 - (CH₂)₀₋₁C(O)N(R⁵)(R⁵);
- wherein phenyl and heteroaryl are optionally substituted with one to three groups independently selected from R³; and alkyl and heterocyclyl are optionally substituted with one to three groups independently selected from R³ and oxo.

7. The compound of Claim 6 wherein heteroaryl is selected from the group consisting of pyridyl, pyrazinyl, pyrimidinyl, triazolyl, tetrazolyl, thiadiazolyl, oxadiazolyl, pyrazolyl, and imidazolyl.

8. The compound of Claim 1 wherein Y is selected from the group consisting of
- C₁₋₈ alkyl,
 - C₂₋₆ alkenyl,
 - (CH₂)C₃₋₈ cycloalkyl,
 - (CH₂)-phenyl,
 - (CH₂)-naphthyl,
 - (CH₂)-heterocyclyl, and
 - (CH₂)-heteroaryl;
- wherein phenyl, naphthyl, and heteroaryl are optionally substituted with one to three groups independently selected from R³; and (CH₂), alkyl, cycloalkyl, and heterocyclyl are optionally substituted with one to three groups independently selected from R³ and oxo.

9. The compound of Claim 8 wherein Y is selected from the group consisting of

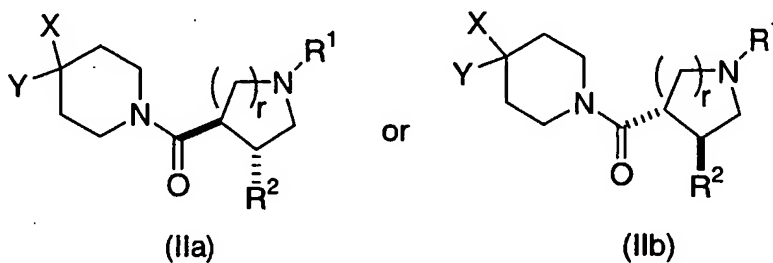
C₁₋₈ alkyl,
C₂₋₆ alkenyl,
C₅₋₇ cycloalkyl, and
phenyl;

wherein phenyl is unsubstituted or substituted with one to three groups independently selected from R³; and alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R³ and oxo.

10. The compound of Claim 9 wherein Y is cyclohexyl or C₁₋₆ alkyl; wherein the cyclohexyl and alkyl groups are unsubstituted or substituted with one to three groups independently selected from R³ and oxo.

11. The compound of Claim 1 wherein r is 1 or 2 and s is 1.

12. The compound of Claim 1 of structural formula IIa or IIb of the indicated *trans* relative stereochemical configuration:



or a pharmaceutically acceptable salt thereof;
wherein

r is 1 or 2;

n is 0, 1, or 2;

p is 0, 1, or 2;

R¹ is hydrogen, amidino, C₁₋₄ alkyliminoyl, C₁₋₆ alkyl, C₅₋₆ cycloalkyl,

(CH₂)₀₋₁ phenyl, or (CH₂)₀₋₁ heteroaryl; wherein phenyl and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R³; and alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R³ and oxo;

5

R² is phenyl or thienyl optionally substituted with one to three groups independently selected from R³;

R³ is selected from the group consisting of

- 10 C₁₋₆ alkyl,
 (CH₂)_n-phenyl,
 (CH₂)_n-naphthyl,
 (CH₂)_n-heteroaryl,
 (CH₂)_n-heterocyclyl,
 15 (CH₂)_nC₃₋₇ cycloalkyl,
 halogen,
 OR⁴,
 (CH₂)_nN(R⁴)₂,
 (CH₂)_nC≡N,
 20 CO₂R⁴,
 C(R⁴)(R⁴)N(R⁴)₂,
 NO₂,
 (CH₂)_nNR⁴SO₂R⁴
 (CH₂)_nSO₂N(R⁴)₂,
 25 (CH₂)_nS(O)_pR⁴,
 (CH₂)_nNR⁴C(O)N(R⁴)₂,
 (CH₂)_nC(O)N(R⁴)₂,
 (CH₂)_nNR⁴C(O)R⁴,
 (CH₂)_nNR⁴CO₂R⁴,
 30 CF₃,
 CH₂CF₃,
 OCF₃, and
 OCH₂CF₃;

in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to two substituents independently selected from halogen, hydroxy, C₁₋₄ alkyl, trifluoromethyl, and C₁₋₄ alkoxy; and (CH₂)_n is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy,
5 and C₁₋₄ alkyl;

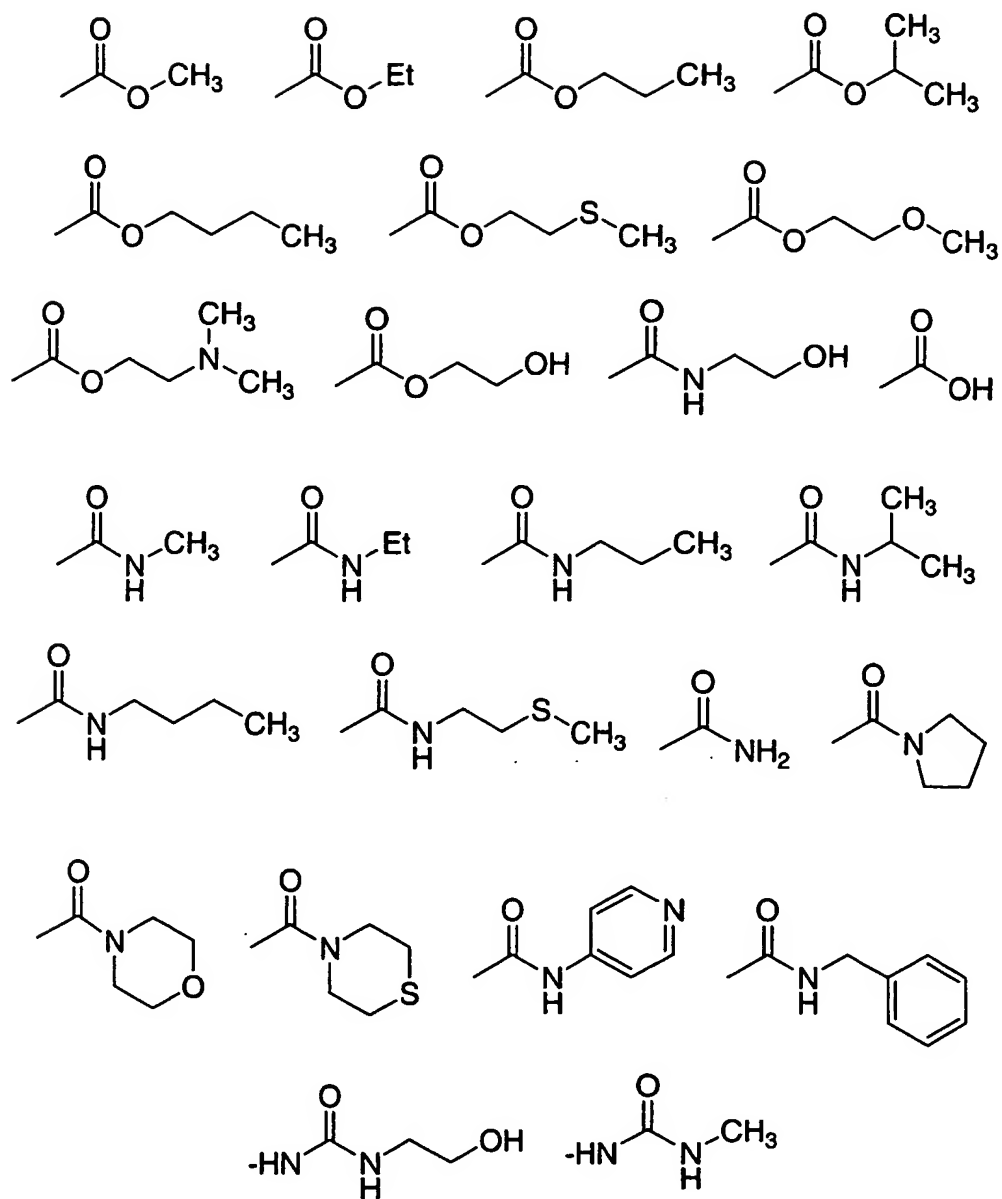
each R⁴ is independently selected from the group consisting of
hydrogen,
C₁₋₈ alkyl, and
10 C₃₋₆ cycloalkyl;

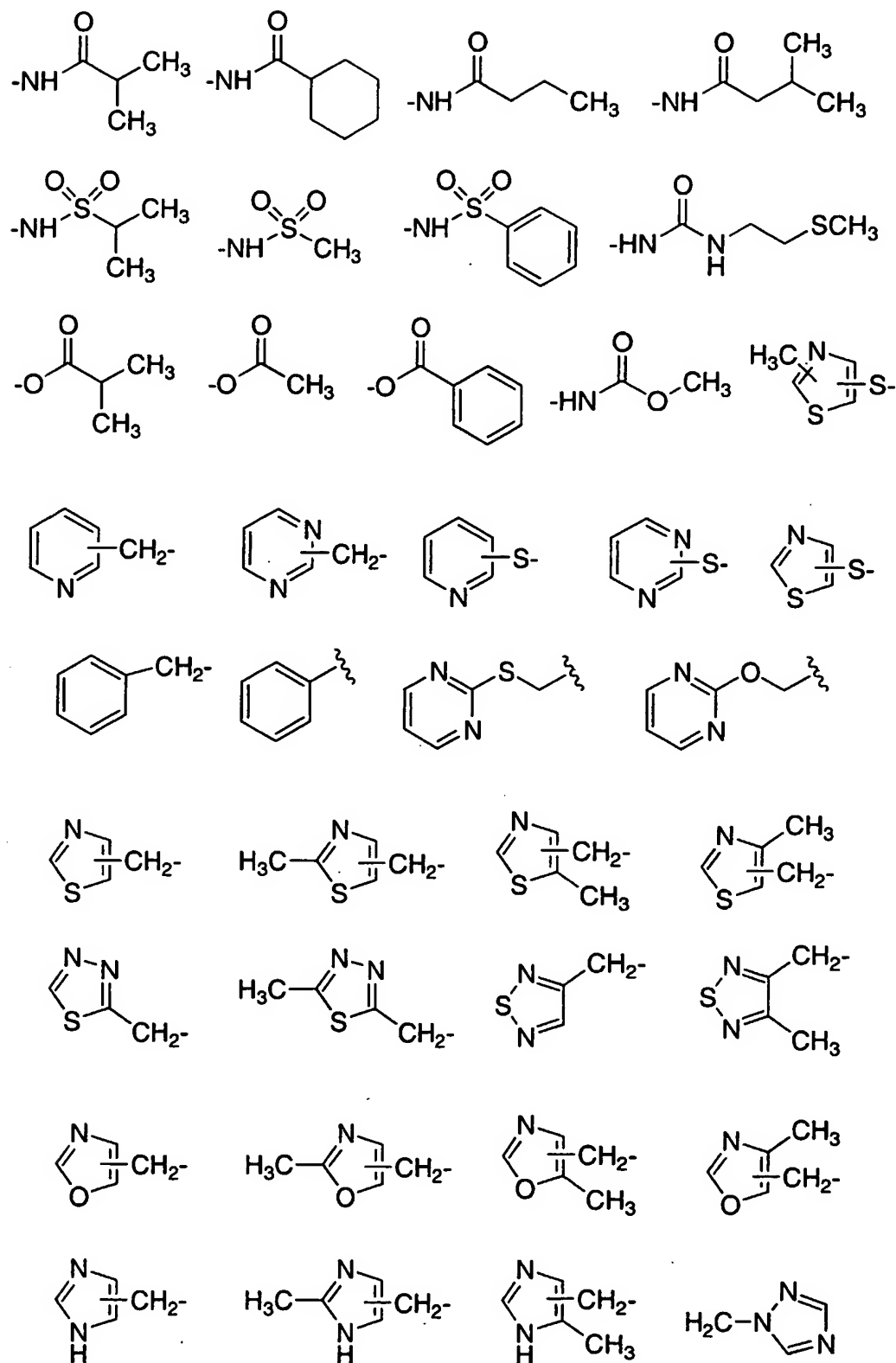
wherein cycloalkyl is unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, and C₁₋₄ alkoxy;
or two R⁴ groups together with the atom to which they are attached form a 4- to 8-
membered mono- or bicyclic ring system optionally containing an additional
15 heteroatom selected from O, S, and NC₁₋₄ alkyl;

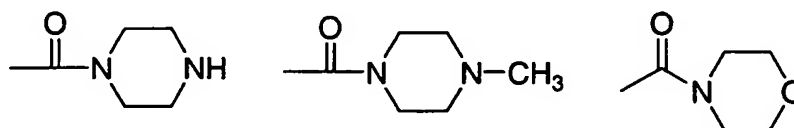
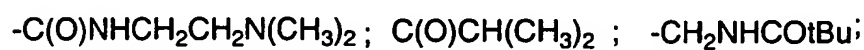
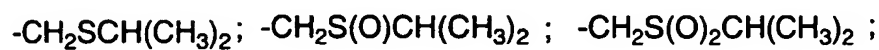
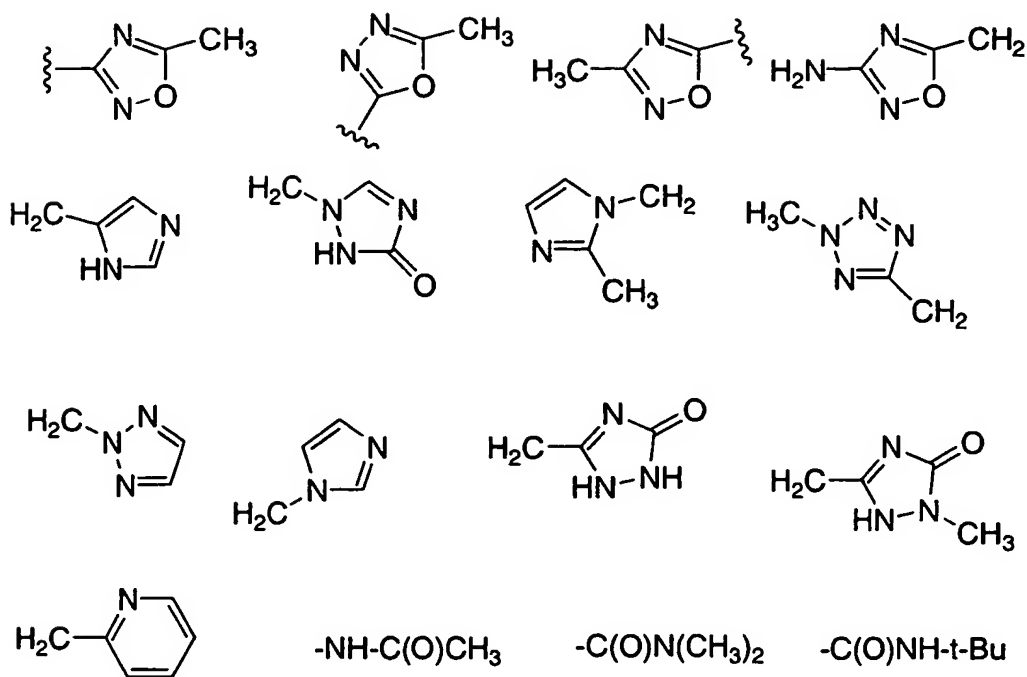
Y is selected from the group consisting of
C₁₋₈ alkyl,
C₂₋₆ alkenyl,
20 (CH₂)₀₋₁C₃₋₈ cycloalkyl,
(CH₂)₀₋₁-phenyl,
(CH₂)₀₋₁-naphthyl, and
(CH₂)₀₋₁-heteroaryl;

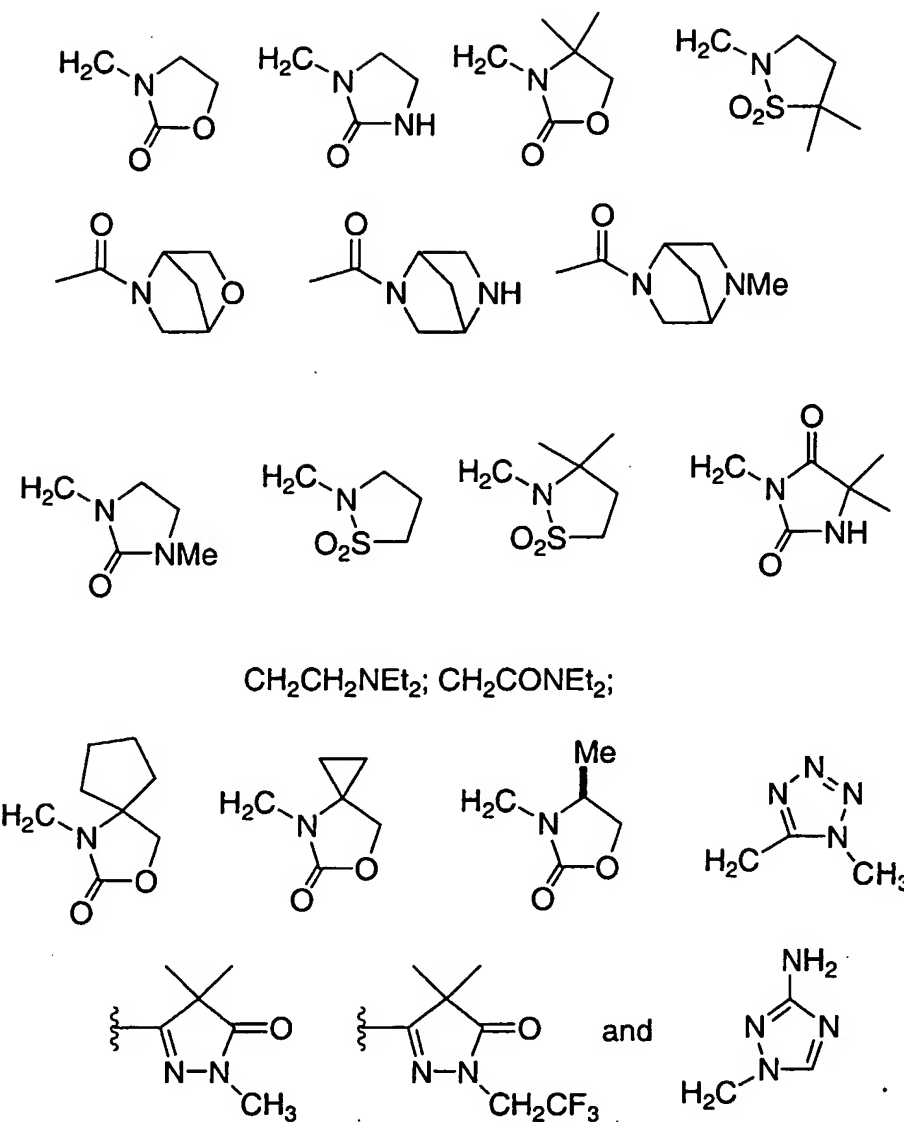
wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to
25 three groups independently selected from R³; and alkyl, (CH₂), and cycloalkyl are
unsubstituted or substituted with one to three groups independently selected from R³
and oxo; and

X is selected from the group consisting of:
30

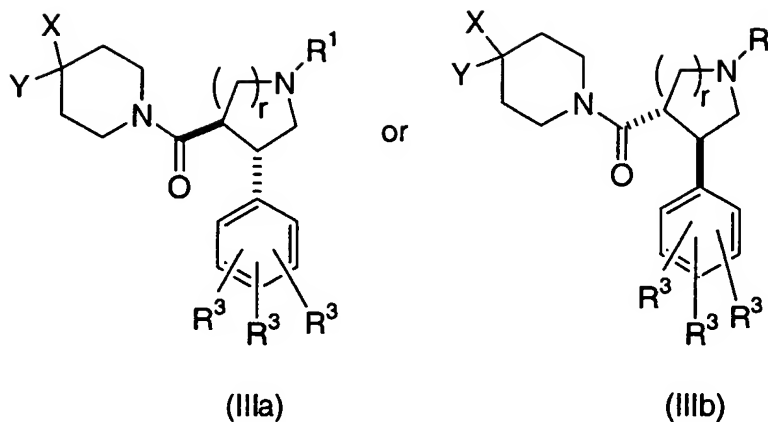








5 13. The compound of Claim 1 of structural formula IIIa or IIIb of
the indicated *trans* relative stereochemical configuration:



or a pharmaceutically acceptable salt thereof;

wherein

r is 1 or 2;

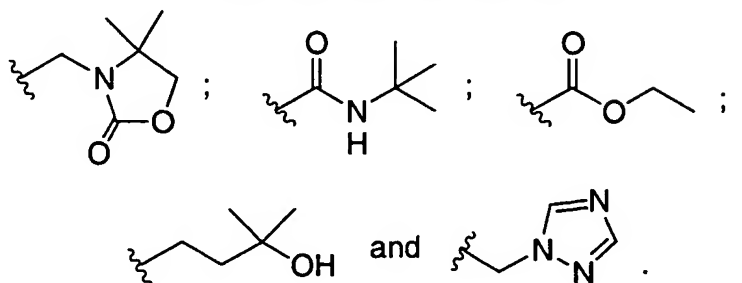
5 R^1 is hydrogen, C₁₋₄ alkyl, or (CH₂)₀₋₁ phenyl;

each R^3 is independently selected from the group consisting of hydrogen, halo, C₁₋₄ alkyl, trifluoromethyl, and C₁₋₄ alkoxy;

Y is cyclohexyl or phenyl; and

X is selected from the group consisting of

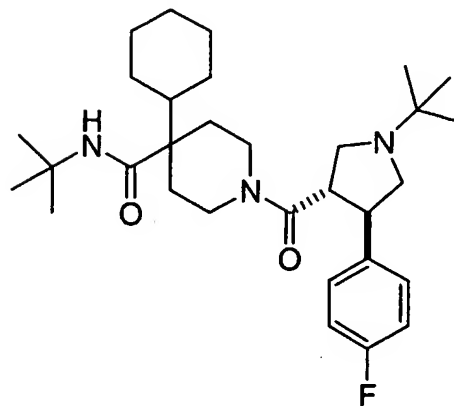
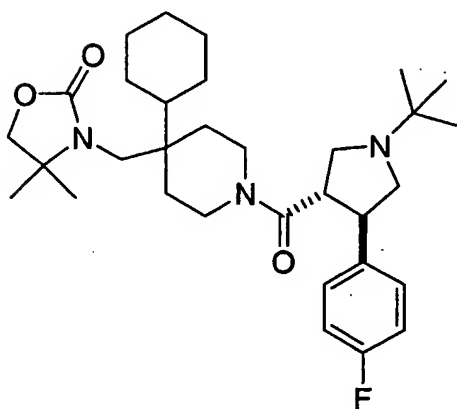
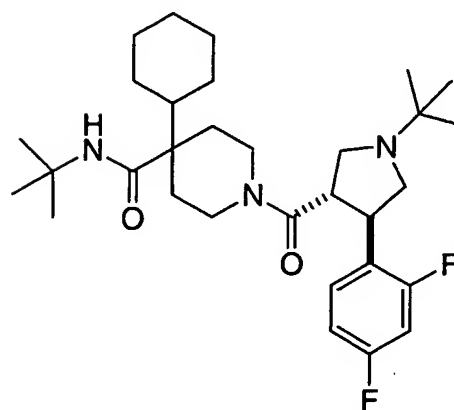
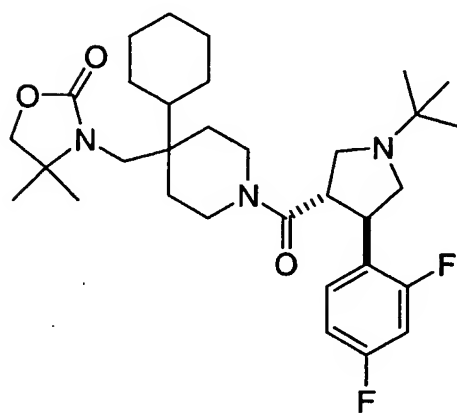
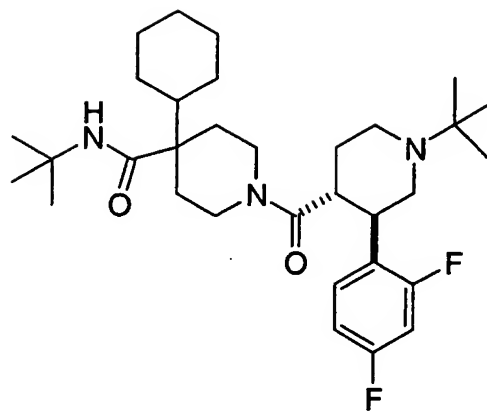
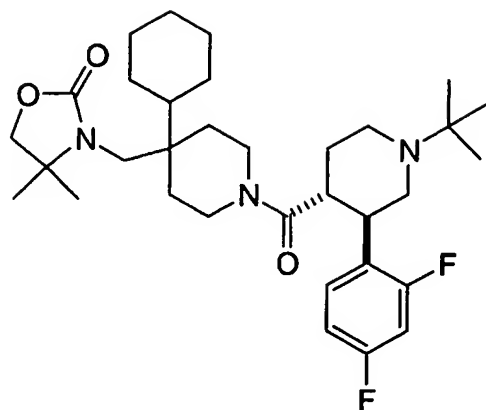
CH₂CH₂NEt₂; CH₂CONEt₂;

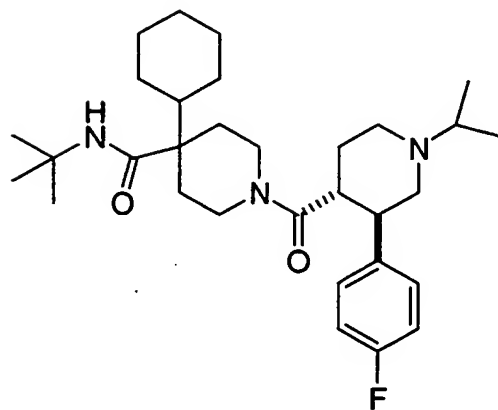
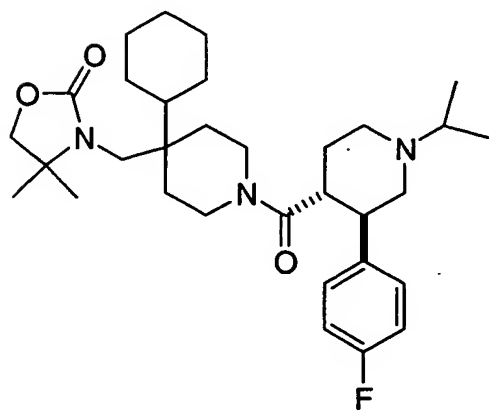
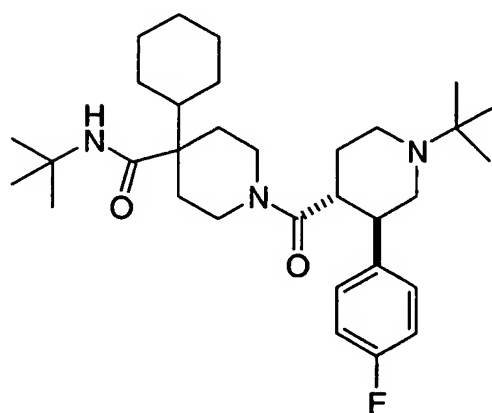
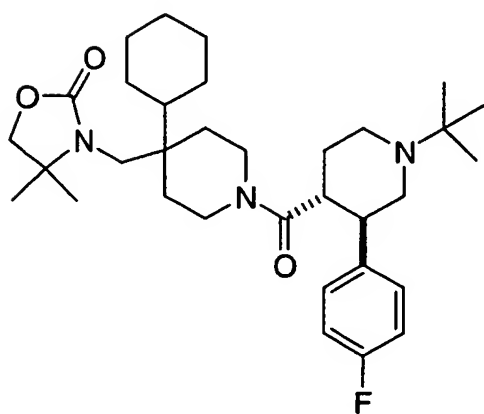
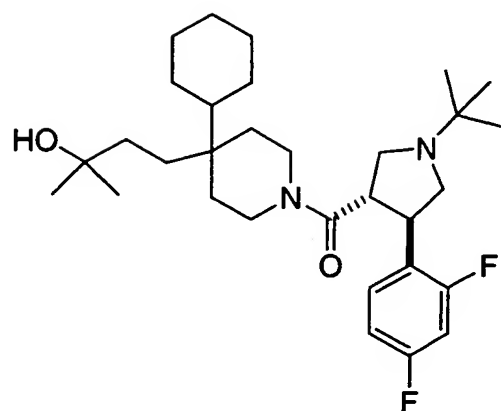
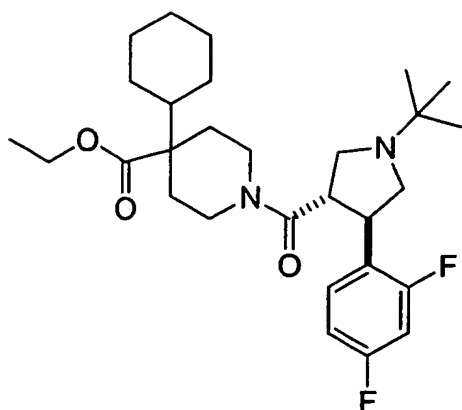


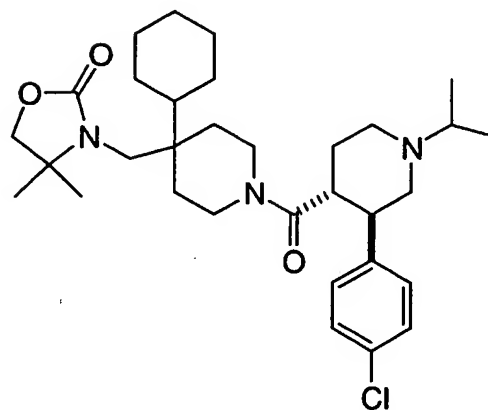
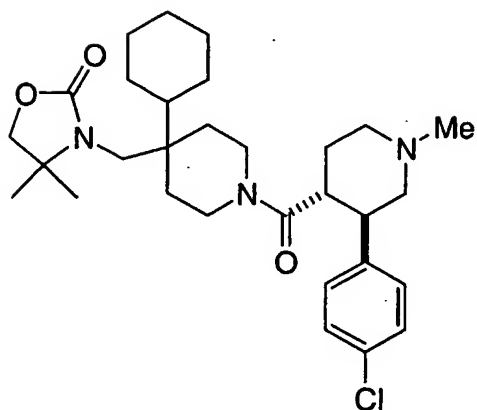
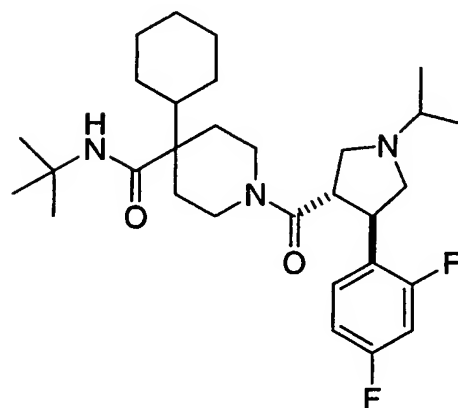
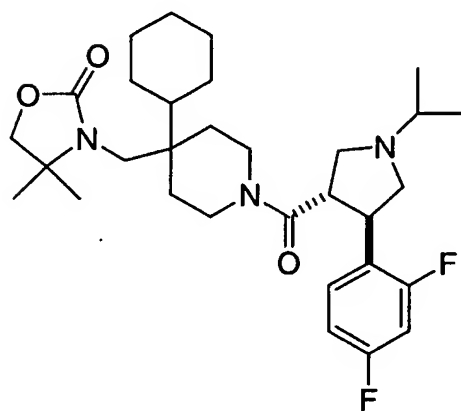
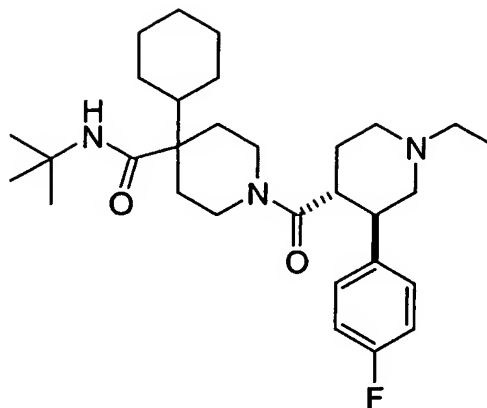
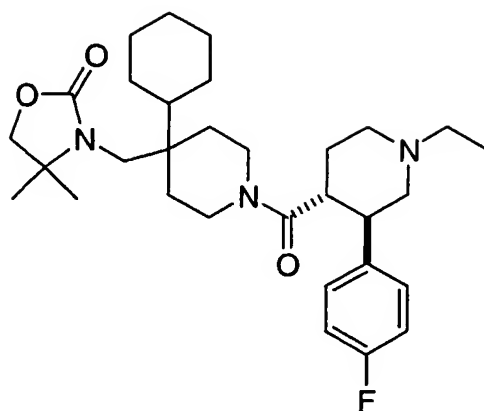
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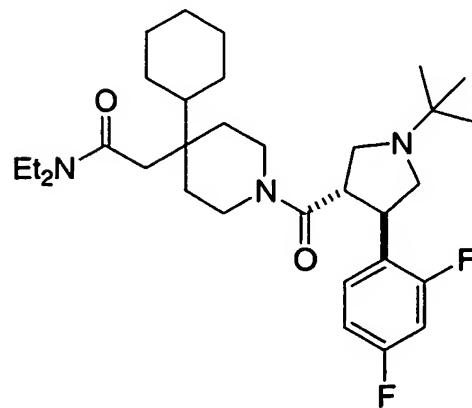
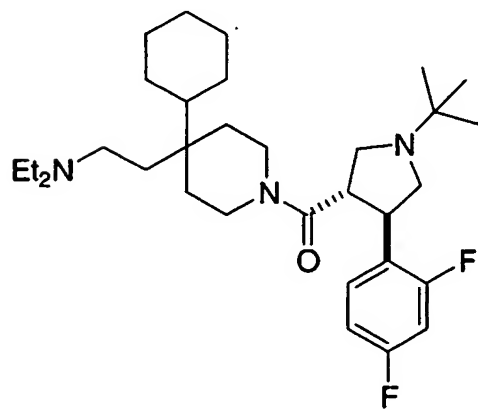
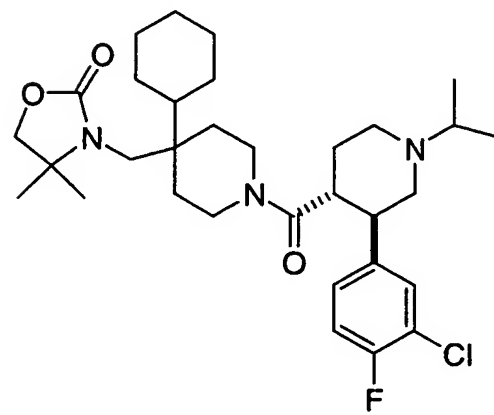
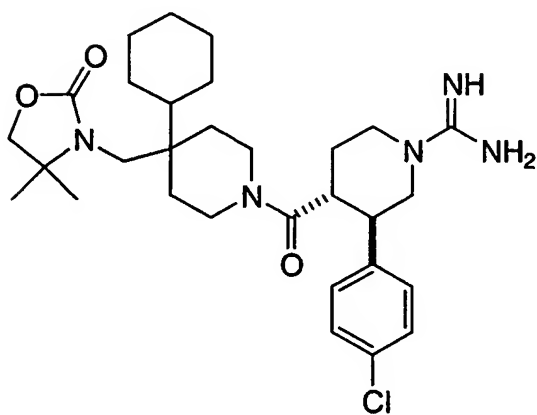
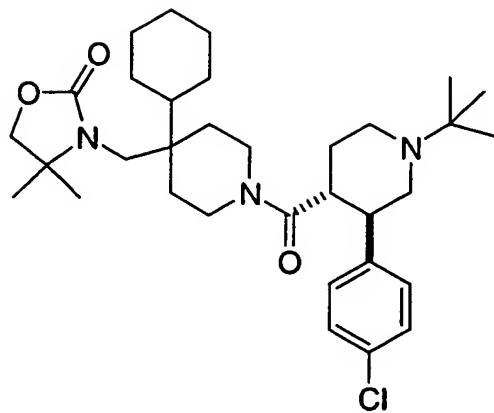
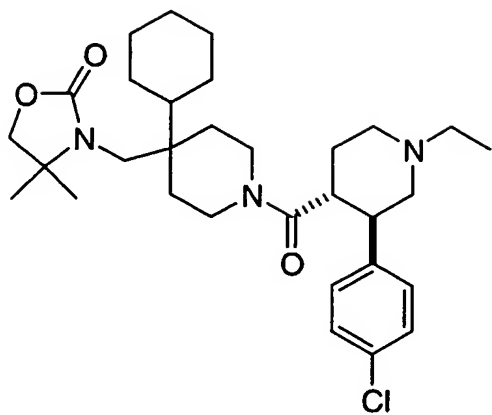
14. The compound of Claim 13 selected from the group consisting

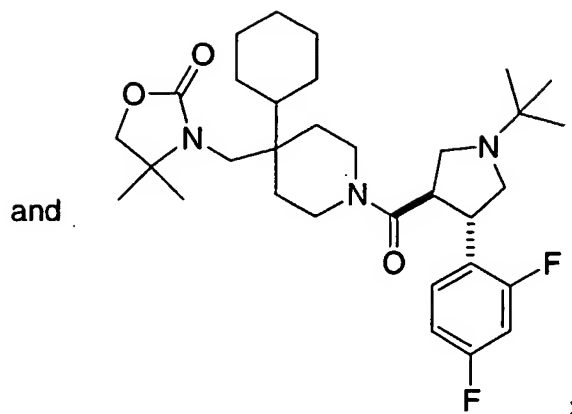
of:











or a pharmaceutically acceptable salt thereof.

15. A method for the treatment or prevention of disorders, diseases
5 or conditions responsive to the activation of the melanocortin receptor in a subject in
need thereof which comprises administering to the subject a therapeutically or
prophylactically effective amount of a compound according to Claim 1.

16. A method for the treatment or prevention of obesity in a subject
10 in need thereof which comprises administering to the subject a therapeutically or
prophylactically effective amount of a compound according to Claim 1.

17. A method for the treatment or prevention of diabetes mellitus
15 in a subject in need thereof comprising administering to the subject a therapeutically
or prophylactically effective amount of a compound according to Claim 1.

18. A method for the treatment or prevention of male or female
sexual dysfunction in a subject in need thereof comprising administering to the
subject a therapeutically or prophylactically effective amount of a compound
20 according to Claim 1.

19. A method for the treatment or prevention of erectile
dysfunction in a subject in need thereof comprising administering to the subject a
therapeutically or prophylactically effective amount of a compound according to
25 Claim 1.

20. A pharmaceutical composition which comprises a compound of Claim 1 and a pharmaceutically acceptable carrier.

21. The pharmaceutical composition of Claim 20 further comprising a second active ingredient selected from the group consisting of an insulin sensitizer, an insulin mimetic, a sulfonylurea, an α -glucosidase inhibitor, an HMG-CoA reductase inhibitor, an anti-obesity serotonergic agent, a β 3 adrenoreceptor agonist, a neuropeptide Y1 or Y5 antagonist, a pancreatic lipase inhibitor, and a cannabinoid CB1 receptor antagonist or inverse agonist.

10

22. The pharmaceutical composition of Claim 20 further comprising a second active ingredient selected from the group consisting of a type V cyclic-GMP-selective phosphodiesterase inhibitor, an α 2-adrenergic receptor antagonist, and a dopaminergic agent.

15

23. A method of treating erectile dysfunction in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the composition of Claim 22.

20

24. A method of treating erectile dysfunction in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of Claim 1 in combination with a type V cyclic-GMP-selective phosphodiesterase inhibitor, an α 2-adrenergic receptor antagonist, or a dopaminergic agent.

25

25. A method of treating diabetes or obesity in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of Claim 1 in combination with an insulin sensitizer, an insulin mimetic, a sulfonylurea, an α -glucosidase inhibitor, an HMG-CoA reductase inhibitor, an anti-obesity serotonergic agent, a β 3 adrenoreceptor agonist, a neuropeptide Y1 or Y5 antagonist, a pancreatic lipase inhibitor, or a cannabinoid CB1 receptor antagonist or inverse agonist.

30

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(54) Title: ACYLATED PIPERIDINE DERIVATIVES AS MELANOCORTIN-4 RECEPTOR AGONISTS

(57) Abstract: Certain novel 4-substituted N-acylated piperidine derivatives are agonists of the human melanocortin receptor(s) and, in particular, are selective agonists of the human melanocortin-4 receptor (MC-4R). They are therefore useful for the treatment, control, or prevention of diseases and disorders responsive to the activation of MC-4R, such as obesity, diabetes, sexual dysfunction, including erectile dysfunction and female sexual dysfunction.

WO 02/068387 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/05623

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/212, 213, 255, 307, 318, 321, 326, 340; 546/139, 194, 198, 208, 256; 544/372; 540/594, 602

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS--structure

EAST/West--subclass, melanocortin

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,166,037 A(BUDHU et al.) 26 December 2000, see col 116, lines 45-50 compound and col. 71, formula XX.	1-12
A,E	US 6,350,760 B1(BAKSHI et al.) 26 FEBRUARY 2002, see entire document.	1-25
A,P	WO 01/070708 A1(MERCK & CO., INC.) 27 SEPTEMBER 2001, see entire article, especially pages 117-182.	21-25
A,P	WO 01/091752 A1(MERCK & CO., INC.) 06 December 2001, see entire document, especially pages 38-43.	21-25

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents	* Later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Z" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

10 JUNE 2002

Date of mailing of the international search report

04 SEP 2002

 Name and mailing address of the ISA/US
 Commissioner of Patents and Trademarks
 Box PCT
 Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

CELIA CHANG

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/05623

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (7):

A61K 31/47, 55, 435, 445, 495; C07D 211/68, 217/02, 223/16, 401/06, 403/08

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/212, 213, 255, 307, 318, 321, 326, 340; 546/139, 194, 198, 208, 256; 544/372; 540/594, 602

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-20, drawn to compounds, composition thereof and method of use thereof.

Group II, claims 21, 25, drawn to composition of multiple active ingredients and method of use such to treat diabetes.

Group III, claims 22-24, drawn to composition of multiple active ingredients and method of treating erectile dysfunction.

The inventions listed as Groups I-III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: patentability of group I depends on the merit of the structure of the compounds. Patentability of groups II or III depending on the quantitative relationship of the specific active ingredients, route and site of administration of each or combination of the active ingredients and their cumulative, enhancement or interrelated effect of the particular active ingredients.

Therefore, special technical feature corresponding to groups I-III is lacking.

CORRECTED VERSION

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- (74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
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